

DEPARTMENT OF WOMEN'S AND CHILDREN'S HEALTH

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HEALTH ECONOMIC ASPECTS OF CERVICAL CANCER SCREENING

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ABSTRACT

Healthcare reform and rising costs are driving demand for resource efficiency to facilitate better-informed healthcare decisions. Health economics represent an interdisciplinary set of tools and concepts to assess the value of everyday decisions, taken in complex healthcare settings, to improve healthcare. Many alternative screening methods are currently available, but knowledge about costs and the value of potential health gains is inadequate.

The aims of the thesis were to study the efficiency in the allocation of resources to cervical cancer screening of importance for setting priorities: the cost of the most prevalent Human Papillomavirus (HPV) related diseases namely cervical dysplasia, cervical cancer and genital warts, modeling the cost-effectiveness of cervical cancer screening and exploring knowledge of HPV, compliance with screening and its correlates.

In one study, we estimated the costs from a societal perspective, of the HPV-related diseases namely cervical dysplasia, cervical cancer and genital warts. Results provided an estimate of €108 million annually showing a significant economic burden on the Swedish welfare system appointed by the most prevalent HPV-related diseases attributable to HPV 6, 11, 16 and 18 infections.

A Markov model was developed to simulate the natural history of HPV, cervical dysplasia and cervical cancer to project the cost-effectiveness of HPV self-sampling within the framework of the Swedish organized screening program. Projected results showed that screening with conventional cytology up to age 35 and thereafter screening with HPV self-sampling at home with five-year time intervals between screening opportunities is potentially cost-effective compared with either no screening or with current cytology based screening practice.

A decision analytic model was developed to evaluate cost-effectiveness of follow-up with HPV triage compared with repeat cytology and immediate colposcopy with biopsy on women with index smear diagnosis of ASCUS and LSIL within the Swedish organized screening program. Model results showed that immediate colposcopy with biopsy was a cost effective follow-up strategy compared with the alternatives. Given the improvement in HPV testing techniques at lower costs, HPV triage can become a cost-effective alternative for follow-up of minor cytological abnormalities.

A descriptive study approach was used to assess possible barriers to and facilitators of cervical cancer screening by estimating time and travel costs and other direct non-medical costs incurred in clinic-based screening, investigating compliance with screening and reasons for noncompliance, determining women's knowledge of human papillomavirus (HPV), and investigating correlates of HPV knowledge and compliance with screening. Via self-administered questionnaires, data were obtained from 1 510 women attending the Swedish organized cervical cancer screening program. The study concluded that time and travel costs of clinic-based screening can be substantial, may influence overall cost effectiveness of

screening programs and constitute barriers to screening. Women with knowledge of HPV and who did not take time off work to attend screening were more likely to comply with screening.

Altogether, this thesis has contributed new health economic data on the societal cost of HPV related diseases; cervical dysplasia, cervical cancer and genital warts on a national level, and patient-level data of indirect costs and other direct non-medical costs for women attending the Swedish organized screening program. This together with data on women's knowledge about HPV and their compliance with screening are valuable information for further policy decisions on revising the organized screening program. By assessing the impact of HPV-related diseases in terms of costs is one important step towards efficient allocation of resources to reduce the economic burden of these diseases. These data are also valuable contribution to economic evaluations, providing information for resource allocation when choosing among different screening methods to reduce disease burden, as well as contributing to knowledge of compliance with population-based preventive health programs.

LIST OF SCIENTIFIC PAPERS

- I. Östensson E, Fröberg M, Hjerpe A, Zethraeus N, Andersson S. Economic analysis of human papillomavirus triage, repeat cytology, and immediate colposcopy in management of women with minor cytological abnormalities in Sweden. *Acta Obstetricia et Gynecologica*. 2010 Oct;89(10):1316-25.
- II. Östensson E, Hellström A-C, Hellman K, Gustavsson I, Gyllensten U, Wilander E, Zethraeus N, Andersson S. Projected cost-effectiveness of repeat high-risk human papillomavirus testing using self-collected vaginal samples in the Swedish cervical cancer screening program. *Acta Obstetricia et Gynecologica*. 2013 Jul;92(7):830-40.
- III. Östensson E, Adler S, Elfström K.M, Sundström K, Zethraeus N, Andersson S. Barriers to and facilitators of compliance with clinic-based cervical cancer screening: population-based cohort study of women aged 23-60 years.
In manuscript, to be submitted in PLOS ONE journal
- IV. Östensson E, Fröberg E, Leval A, Hellström A-C, Bäcklund M, Zethraeus N, and Andersson S. Cost of preventing, managing and treating human papillomavirus (HPV)-related diseases before the introduction of quadrivalent HPV vaccination.
In manuscript, to be submitted in PLOS ONE journal

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LIST OF ABBREVIATIONS

AIS	Adenocarcinoma in situ
ASC-H	Atypical squamous cells- HSIL can be ruled out
ASC-US	Atypical squamous cells-uncertain significance
CC	Conventional cytology
CI	Confidence interval
CIN	Cervical Intraepithelial Neoplasia
CIS	Cancer in situ
FIGO	International Federation of Gynecology and Obstetrics
EQ-5D	EuroQol 5 dimensions
HPV	Human Papillomavirus
HR HPV	High-Risk HPV
HRQL	Health-related quality of life
HSIL	High-grade squamous intraepithelial lesions
IARC	International Agency for Research on Cancer
ICC	Invasive cervical cancer
ICER	Incremental cost effectiveness ratio
LBC	Liquid based cytology
LEEP	Loop electrosurgical excision procedure
LSIL	Low-risk squamous intraepithelial lesions
LYG	Life-years-gained
NPV	Negative predictive value
PCR	Polymerase chain reaction
PPV	Positive predictive value
QALY	Quality-adjusted life year
QoL	Quality of Life
SCC	Squamous cervical cancer
SCJ	Squamocolumnar junction
SEK	Swedish kronor
SES	Socio economic status
STI	Sexual transmitted infection

TBS	The Bethesda system
TZ	Transformation zone
WHO	World Health Organization
WTP	Willingness to pay

1 INTRODUCTION

Cervical cancer (CC) is preventable through screening and vaccination programs, but many challenges remain before such programs become fully effective, with the potential to fully eradicate the disease using new methods and future technology. Organized screening has already reduced cervical cancer incidence and mortality in Sweden since the program was introduced in the 1960s. Worldwide, cervical cancer is still the third most common cancer among women, exceeded only by breast cancer and colon cancer; 85% of CC occurs in countries that lack organized screening. Statistics show that the incidence of squamous cell carcinoma (SCC) is stagnating, while the incidence of adenocarcinoma (ADC) is increasing. The newly developed Human Papillomavirus (HPV) test is more sensitive than the conventional Pap smear. The introduction of Liquid-based cytology made sample processing easier and increased laboratory efficiency, but sensitivity for detecting CIN2+ is still inferior compared with Pap smear testing in primary screening. The ongoing debate of whether to change from cytology (Pap smear) to HPV testing in primary screening could alter screening program protocols: longer screening intervals, triage testing with cytology for HPV-positive women and new screening algorithms for management of HPV-positive and cytology-negative women. Further, availability of HPV self-sampling devices could be offered to women who do not comply with the current clinic-based screening program. However, questions still remain about how to include all women, including hard-to-reach women, in the screening program, what actions to take to reduce potential over-diagnosis and over-treatment of regressive disease, and how to reduce adverse outcomes. According to National Board of Health and Welfare [Socialstyrelsen] guidelines, decision-makers in Sweden need to ascertain both clinical effectiveness and cost-effectiveness before introducing new screening programs, or revising the existing population-based screening program. Given that compliance with cervical cancer screening is crucial to both the clinical effectiveness and cost effectiveness of screening, identification of potential barriers is particularly important. This and evaluation of new screening technologies is extremely important. Convention holds that cost-effectiveness is assessed from a societal perspective, including all costs imposed on society. Depending on the employment circumstances of the individual, screening attendance may lead to loss of income. This factor, along with the individually perceived high value for time and travel costs and other direct non-medical costs, could deter use of screening services. Determining whether costs for time and travel incurred by women to attend screening have impact on compliance will strengthen the evidence base for the organized screening program. Even though globally HPV is one of the most common sexually transmitted infections (STIs), general awareness of HPV is low. By determining the extent of this knowledge gap within the population eligible for screening, invaluable information could be made available to public health workers to enable them to deliver a consistent health message and to educate the public.

The aims of the thesis were to study the efficiency in the allocation of resources to cervical cancer screening of importance for setting priorities: the cost of the most prevalent HPV related diseases; cervical dysplasia, cervical cancer and genital warts, modeling the cost-effectiveness of cervical cancer screening and exploring knowledge of HPV, compliance with screening and its correlates. By doing so, we shall contribute with information to facilitate better-informed decisions when revising the organized cervical cancer screening program.

2 BACKGROUND

2.1 CERVICAL CANCER

Invasive cervical cancer is a malignancy that occurs in the epithelium of the cervix (1). About 80%-95% of all cervical cancer is classified as squamous cell carcinoma (SCC), followed by adenocarcinoma (ADC) (5-20%) (2).

2.1.1 The cervix

The cervix, which connects the vagina and the uterus, consists of dense fibromuscular tissue and is about 2 cm in diameter and 3 cm long. The cervix consists of two main portions. The ectocervix is the outer portion of the cervix that can be visualized from inside the vagina during speculum examination. The endocervix is the inner portion of the cervix. The opening in the center of the ectocervix, known as the external os, allows passage between the uterus and the vagina. The endocervical canal is a tunnel through the cervix, from the external os into the uterus.

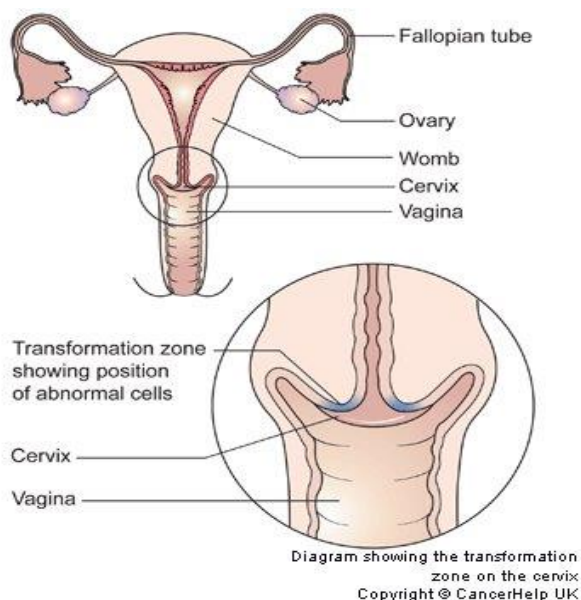


Figure1. Cervix and the transformation zone (TZ)

(Adapted from <http://www.cancerresearchuk.org/cancer-help/type/cervical-cancer/about/the-cervix>)

The transformation zone (TZ) is the area between the original and the new squamocolumnar junction (SCJ). The original SCJ remains un-changed until puberty. Post puberty, forming of the functional junction occurs and is termed the new SJC. The area between the original and new SCJ occupies by the TZ and expands toward the cervical opening with increasing age (3). Cervical cancer arises from the TZ, which is susceptible to oncogenic HPV-induced neoplastic transformation (1). Persistent infections with HPV can cause precancerous lesions known as cervical intraepithelial neoplasia (CIN). Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) is preceded by CIN (4).

2.1.2 Natural history of HPV infection, CIN and cervical cancer

Today it is widely accepted that HPV is the major causal factor in all cervical cancers, which likely makes the disease the most common virally-induced cancer (5, 6). HPV infection is common among both men and women and is transmitted through sexual activity. HPV infection usually clears without treatment, though in some cases the infection persists and may progress to precancerous changes (i.e., cervical intraepithelial neoplasia (CIN) that are classified according to the proportion of “cervical epithelial cells” showing abnormalities and degree of atypia: CIN 1 (mild dysplasia), CIN2 (moderate dysplasia) and CIN 3 (severe dysplasia). If undetected and left untreated, CIN3 precancerous lesions may progress to invasive cervical cancer (7). Precancerous lesions are amenable to detection through screening due to the time of approximately one decade generally required for transformation from precancerous lesions into cervical cancer.

Human papillomavirus infection and related diseases

Human papillomavirus (HPV) is a DNA virus from the papillomavirus family that causes productive infections in the keratinocytes of the skin or mucous membranes (8). Most HPV infections are asymptomatic. However, nononcogenic HPV infections (low risk (LR-HPV)) such as types 6 and 11 may cause benign papillomas, including warts or squamous cell papillomas, while infection with oncogenic HPV (high risk (HR-HPV)) can cause cancers of the cervix, vulva, vagina, penis, oropharynx and anus (9). Retrospective studies have shown that almost 100% of cervical cancer cases were HR-HPV-positive. HPV infection is sexually transmitted between both men and women and has been insensitive to general improvements in medical care and living standards. Therefore, vaccination and organized screening programs can prevent HPV epidemics and therefore cancer within a population.

According to a study by Söderlund-Strand et al., 2013, 44 146 samples from sexually active adolescents were submitted for Chlamydia trachomatis testing in southern Sweden and showed that HPV positivity peaked at 54.4% [95% confidence interval (CI), 52.2-56.6] among 21-year-old women and at 15.0% (95% CI, 12.4-17.6) among 23-year-old men. HPV positivity was 37.8% (95% CI, 37.3-38.3) for women and 11.2% (95% CI, 10.6-11.8) for men. The most prevalent types in descending order among women were: HPV 16 (10.0%; 95% CI, 9.7-10.3) and HPV 51 (6.0%; 95% CI, 5.7-6.3), and among men: HPV 16 (2.1%; 95% CI, 1.8-2.4) and HPV 51 (1.7%; 95% CI, 1.5-1.9) (10). In another review, prevalence among men was reported at 1.3%-72.9% in studies where multiple anatomic sites or specimens were evaluated, 56% of which reported $\geq 20\%$ HPV prevalence (11). According to a meta-analysis of studies published between 1995 and 2009 that used polymerase chain reaction or Hybrid Capture 2 to detect HPV in women with normal cytological findings, the most prevalent HR-HPV types in women with normal cytology were HPV16 (3.2%), HPV 18 (1.4%), HPV51 (0.9%), HPV31 (0.8) and HPV58 (0.7%), with other types representing about 0.6% (12). However, it is important to note that the distribution of HPV types may vary between populations and between different assays (12).

Despite regional variations among different populations, HPV is the most common sexually transmitted infection (STI) in the world with a prevalence of 11-12% in women with normal

cytology. The majority of HPV infections are transient; 70%-75% clear within 1 year (13) and approximately 90% clear within 2 years (14, 15). Among HPV-infected women, 50%-55% show evidence of an immune response (16). Previous research suggests that the low antibody titers resulting from natural HPV infection do not provide full protection against future HPV infection (17). Persistent oncogenic HPV infection significantly increases the risk for development of cervical precancerous lesions and cervical cancer (18, 19). HPV prevalence increases in proportion to severity of lesions, from 12.6% in women with normal cytology to 90% in women with CIN grade 3 (CIN3) and invasive cervical cancer (ICC) (12). The highest prevalence among women is found within their first years after sexual debut. One study reported the prevalence of HPV genotypes 6, 11, 16, and 18 in young women to be 11.4 %, with the highest rate in the youngest age group (18.1 % in the 11-19 years, 12.5 % in the 20-24 years, and 7.0 % in the 25-29 years) (20). One study that used vaginal swab collection to examine the association between age and prevalence of HPV regarding low risk (LR HPV) and high risk (HR HPV) types among a US sample population (21), showed that 26.8% (95% CI, 23.3%-30.9%) were positive for any HPV DNA and that HPV prevalence increased up to age 20 -24 years and subsequently decreased. However, the prevalence of HPV types 16 and 18 was relatively low. HPV types 6 and 11 (low-risk) and 16 and 18 (high-risk) were detected in 3.4% of individuals, among whom HPV-6 was detected in 1.3%, HPV 11 in 0.1%, HPV 16 in 1.5%, and HPV 18 in 0.8%.

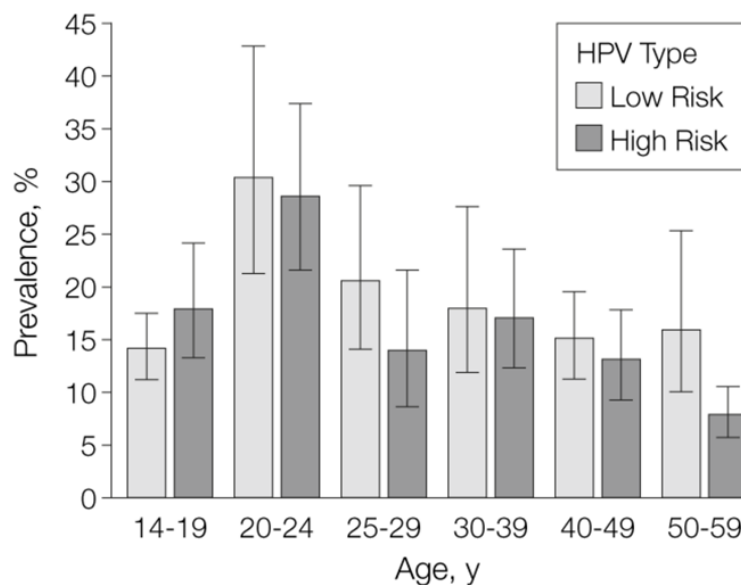
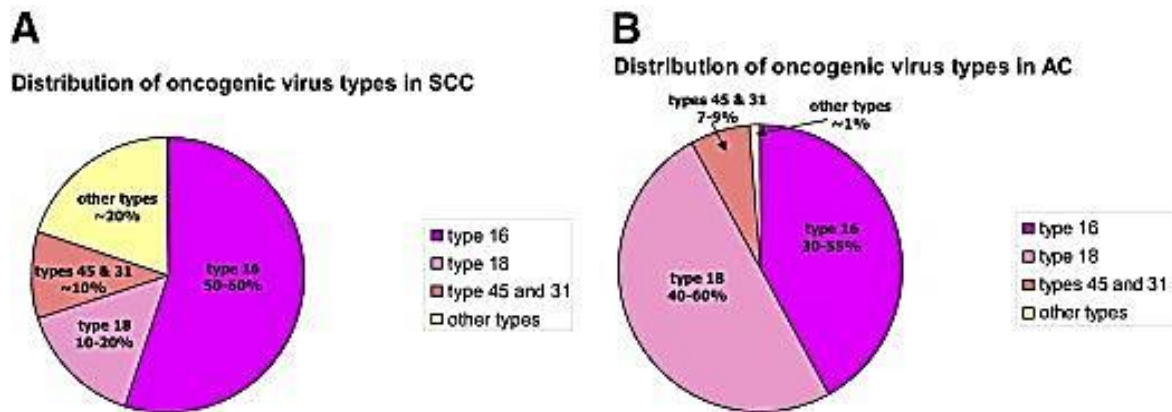


Figure 2. Age and overall prevalence of HPV

“HPV indicates human papillomavirus; NHANES, National Health and Nutrition Examination Survey. Error bars indicate 95% confidence intervals. Both low-risk and high-risk HPV types were detected in some females. Low-risk HPV types are defined as HPV type 6, 11, 32, 40, 42, 44, 54, 55, 61, 62, 64, 71, 72, 74, 81, 83, 84, 87, 89, and 91; and high-risk HPV types as HPV type 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, 85, and IS39.”[Adapted from Dunne et al., 2000]

In 2007, Herzog et al. (3) reported an important difference when comparing distribution of oncogenic HPV types in SCC and ADC. Among women with SCC, oncogenic HPV type 16 (the most prevalent) was found in 50%-60% of cases and oncogenic HPV type 18 was found in 10%-20% of cases. For women with ADC, oncogenic HPV type 18 accounts for an estimated 40%-60% of cases, while oncogenic HPV type 16 was found in 30%-55% of cases.

Figure 3. Distribution of the predominant oncogenic HPV types in SCC and ADC



“A, Global distribution of the predominant oncogenic HPV types in cervical SCCs. B, Global distribution of the predominant oncogenic HPV types in cervical adenocarcinomas. Fuchsia represents type 18; dark pink represents type 16; salmon represents types 45 and 31; yellow represents other types.” [Adapted from Herzog et al., 2007.]

Precancerous lesions of the cervix

Persistent infection with HPV is known to precede cellular neoplasia (8). Precancerous lesions precede both SCC and ADC and are divided and classified into cervical neoplasia (CIN) grades 1, 2 and 3 based on histological appearance. Degree of severity is based on the proportion of atypical cells and architectural disruption, where CIN 1 is mild dysplasia, CIN2 moderate dysplasia and CIN3 severe dysplasia, or equivalent to cancer in situ (CIS). A penetration of the epithelial basement membrane that occurs by atypical cells is defined as invasive cervical cancer (22).

Due to the difficulty in distinguishing among the various CIN grades, the Bethesda system was introduced as a supplementary classification system. It is based on cytology, where CIN 1 is characterized by low grade squamous intraepithelial lesions (LSIL) and where CIN2 and 3 (CIN2+) are characterized by high-grade squamous intraepithelial lesions (HSIL). The Bethesda system also provides nomenclature for the cells that are not able to be classified as LSIL, such as atypical squamous cells with uncertain significance (ASC-US) and atypical squamous cells that can't rule out the possibility of HSIL (ASC-H) (23). The Bethesda system also discriminates between atypical glandular cells not otherwise specified (AGC-NOS), atypical glandular cells that suggest adenocarcinoma in situ (AIS) or cancer (AGC-neoplastic), and adenocarcinoma *in situ* (AIS). AIS precedes invasive cervical adenocarcinoma and occurs below the TZ and is therefore covered by normal metaplastic or dysplastic epithelium. Studies have estimated that the time period required for disease progression from AIS and to ADC is 5-13 years (24, 25).

There is a cumulative risk of developing ICC or CIS related to severity of dysplasia. If CIN 3 is left untreated, the risk of developing ICC has been estimated at 30%-50% based on reviews of studies on follow-up management of women with abnormal cytology between the years 1950 and 1990 (7, 26). However, the majority (88%) of CIN 1 lesions spontaneously regress to normal cytology, while only an estimated 10% of CIN1 progresses to CIN3 or worse over a 10-year time interval. Progression from CIN 2 to CIN 3 was found to occur in 32% of cases over a 10-year period (27). The proportion of HPV positivity increases with severity of cervical lesions. A meta-analysis of 423 PCR-based studies worldwide conducted on a population of women with findings ranging from normal to ICC found no significant differences in HPV type distribution among women with normal cytology, ASCUS, LSIL or CIN1. HPV16 positivity increased with lesion severity, showing a rising trend from normal/ASCUS/LSIL/CIN1 (20-28%), through CIN2/HSIL (40/47%) to CIN3/ICC (58/63%) (28). A broad range of non-HR-HPV types are commonly detected among women with LSIL and HSIL, who demonstrate a high prevalence of multiple infections associated with these lesions (29). Given that infections with HPV types 16 and 18 are causally related to detected lesions even in the co-presence of other HPV types, the protective impact of vaccination against HPV 16 and HPV 18 on cervical lesions can be expected to increase from 17% in ASC-US, through 49% in HSIL and up to 70% in cervical cancer (28).

2.1.3 Diagnose and treatment

Invasive cervical cancer is a malignancy arising from the epithelium of the cervix (1). About 80%-95% of all cervical cancer cases are categorized as squamous cell carcinoma (SCC), followed by adenocarcinoma (ADC) (5-20%) (2). The early stages of cervical cancer are typically asymptomatic. In later stages, abnormal bleeding is the main symptom of invasive cervical cancer. Additional symptoms may occur in advanced stages, including vaginal discharge, pelvic or low back pain, and sciatica. Indications of advanced disease include bowel and urinary symptoms. Any of these symptoms should prompt further clinical examination to obtain a definitive histological diagnosis (30). Women with invasive cervical cancer are immediately referred for clinical examination and FIGO staging (available in English at <http://www.figo.org>), the most common classification system worldwide (30).

Treatment of women with diagnosed FIGO stage

Worldwide, treatment of cervical cancer varies significantly in developed and developing countries. This due to scarce health care resources in developing countries, availability of surgeons skilled in radical pelvic surgery, and the issue of “*fertility-sparing therapy*” in developed nations. Localized cancer is treated with a combination of radical hysterectomy and radiotherapy, while regional and distant cancers are treated with radiotherapy alone (31-33). Patients with FIGO stage 1a1-1b1 are treated with Wertheim-Meigs radical hysterectomy. Stage 1a1 can be treated by simple hysterectomy or conization since the risk of regional lymph node metastasis is very low, while stage 1a2-1b1 is treated with Wertheim-Meigs radical hysterectomy or trachelectomy with pelvic lymph node dissection, given the higher risk of lymph node metastasis. Treatment of patients with FIGO stage II involves

combined radio- and chemotherapy. The difference in treatment between FIGO stage II and FIGO stage III is the number of brachytherapy treatments and the total dose of radiotherapy delivered to the pelvis. In more advanced stages, with a large tumor burden involving the parametrium, patients are treated with a higher dose of radiotherapy to the pelvis and fewer brachytherapy sessions, compared with large bulky central tumors, which require more brachytherapy sessions and a lower total dose of radiotherapy to the pelvis. Treatment of patients with FIGO stage III involves radiotherapy and chemotherapy. Palliative treatment entails chemotherapy alone. The disseminated disease of FIGO stage IV requires different treatment than FIGO stage III, with more chemotherapy and limited radiotherapy delivered only to the gross tumor volume. As per national recommendations, patients are followed for 5 years after treatment, with a total of 13 clinical examinations and 1 MRI after treatment. Thereafter, yearly gynecological examinations throughout women's life are recommended.

Prognosis and survival rates

According to one study, the presence of lymph node metastases was associated with a worse prognosis in ADC than in SCC, but there was no difference in prognosis in the absence of lymph node metastases (34). This was further supported by a literature review (35). Another study presented contradictory evidence, suggesting lower survival rates among patients with ADC in both early and advanced FIGO stages (36). In another study of 1 335 cervical cancer cases detected between January 1, 1999 and December 31, 2001, with an 8.5-year follow-up period, supporting evidence was found indicating no difference in prognosis between ADC and SCC. However, the overall prognosis was better among women detected through screening than women who presented with symptoms (37), mainly because screening often detects disease in the early stages, whereas symptomatic patients often present in late stages.

2.1.4 Quality of life

Survival rate from cervical cancer increasingly depends on early diagnosis and more effective treatments. Consequently, the availability of a valid and reliable general health-related quality of life (HRQL) instrument is important. The HRQL in women diagnosed with cervical cancer provides important data for future preventive programs aimed at improving women's health. Quality of life measures generic outcomes, which are recommended to help assess the cost effectiveness of new preventive programs. HRQL reflects the subjective perceptions and experiences of the individual. Impaired quality of life indicates functional limitations and perceived difficulties in everyday life caused by a disease or illness. HRQL measurements assess patient health on a scale of 0 to 1, where 0 signifies death and 1 perfect health. The EQ-5D instrument summary index score is a standard measure for assessing quality of life, which is used to calculate quality adjusted life years (QALYs) in economic evaluations (38). Population-based social tariffs (health state valuations in the general population) use the EQ-5D instrument to calculate utility weights and patient preference. A previous study confirmed that the EQ-5D questionnaire is valid and

reliable for the assessment of HRQL in patients with cervical cancer in Taiwan (39). Treatment of precancerous and early cervical cancer stages changes patient quality of life. Previous studies have focused on the effect of radical treatment for invasive cervical cancer on the physical and psychological state of women in late stage disease (40-42). One study that addressed the association between HRQL outcomes and survival in a population-based cohort of women diagnosed with invasive cervical cancer found that HRQL outcomes, especially physical function and mental health dimensions, are associated with survival (43). Another study found that the neighborhood context was an influential contributor to survival, suggesting the need for future research on the role of ethnic groups, socio-ecological contexts, stress and medical factors on disease outcomes (44). Further, few studies address sexual activity among women diagnosed with early stage cancer (45). However, the literature shows that women diagnosed with pre-cancer lesions or cancer experienced heightened disease awareness, fear of disease-related death, fear of losing reproductive organs and fertility, anxiety over their future family life, social and professional life – in other words, the quality of life.

2.2 HEALTH ECONOMICS

2.2.1 Health Economics - general issues

The ability to produce treatments and interventions has increased exponentially with introduction of new technologies, while the demand for health care has increased. A consequence, health care costs are increasing and puts a strain on limited health care resources. Unavoidable choices and trade-offs have to be made since there always will be more available technology options that resources will allow. These choices are relevant for public decisions about allocation of resources. Public decisions will have to be made based on formal evaluations if the additional health benefits are worth the additional costs implied with new technology. Health economics is today a commonly used term in medical and scientific literature and policy documents. Over the past decades, there has been a shift from 'passive funding' of health care to concerns about resource costs and the health outcomes achieved from producing health care. The relevant question is often; how much money should we spend on health care and how do we spend it efficiently? Health economic evaluation is a method that has been developed to address this issue and concerned with issues relating to the allocation of scarce resources to improve health (46). This fundamental change of attitude has led to concerns for both effectiveness and cost-effectiveness of innovative technology or interventions, rather than only for efficacy and safety. The acceptability for new technology is now more related to the cost and health benefit of the incremental improvement to the individual.

Definition of health economic evaluation

Health economic evaluation can be defined as “*the comparative analysis of alternative courses of action in terms of both their cost and consequences*”(46). The basic mission of any health economic evaluation is to identify, measure, value and compare the costs and consequences of the various alternatives under consideration in order to determine whether a programme offers “good value for money”.

Types of health economic evaluation

Economic evaluations are normally divided into four different types: *cost-minimisation analysis*, *cost-effectiveness analysis*, *cost-utility analysis* and *cost-benefit analysis* (see Table 1). All methods measure costs in monetary terms, but differ in how the health outcomes are measured (46-48). In general, if the economic question is whether a treatment or intervention is an appropriate use of resources in the specific area of illness, comparison is performed between alike treatments and interventions and the outcome measure can be disease specific (single outcome). Then a cost-effectiveness analysis will be an appropriate type of evaluation. When there is occurrence of multiple outcomes, either a choice of one outcome measure or an index should preferably be constructed. For example, outcomes for interventions for cervical cancer can be survival, remissions, adverse events, quality of life, etc. If the economic

question is whether a treatment or intervention is considered an appropriate investment when considering all diseases, the comparison will be with treatments and interventions in other diseases and outcome measures are generic such as quality-adjusted life year (QALY), an outcome that combines survival and quality of life. Then, this would be a cost-utility analysis which is considered a specific type of cost-effectiveness analysis. However, the most important question is if there is data on clinical evidence existing for the alternative treatments or interventions. The effectiveness data will assess the quality of the economic evaluation. In Table 1, a summary is presented of effectiveness measures used in the different types of economic evaluations with indication on what type of question to address. Also, each of these types is further explained below. Further, the cost-of-illness study (COI), a form of economic analysis which attempts to estimate the economic burden placed up on society for a disease is also discussed further below.

Table 1. Usability and measure of effect in different types of economic evaluations

Analysis	Effectiveness	Usability
Cost-minimization analysis	The effects of alternatives are identical and therefore not measured.	Comparison of costs of treatment(s)/intervention(s) within the same disease
Cost-effectiveness analysis (CEA)	One disease specific measure (e.g. relapses avoided), disease free time, life years saved or an index with multiple measures	Comparison of treatment(s)/intervention(s) within the same disease
Cost-utility analysis (CUA)	Summary measure combining survival and quality of life (e.g. quality of life years (QALYs))	Comparison of treatment(s)/intervention(s) for different diseases
Cost-benefit analysis (CBA)	Effectiveness expressed as monetary benefit (e.g. willingness to pay (WTP))	Comparison of investment in the health sector with investments in other sectors (e.g. road safety or education)

[Adapted from Kobelt 2002 (49)]

Cost-minimization analysis compares interventions based on cost alone and is used when alternative interventions have equivalent health outcomes. The least costly alternative then becomes the preferred approach.

Cost-effectiveness analysis (CEA) assesses both the costs (C) and effects (E) of alternative interventions measured in one-dimensional units, such as life years gained (LYG) or an index with multiple measures. Regarding decisions about resource allocation, the relevant measure in economic evaluation is the *incremental cost effectiveness ratio* (ICER) (see Box 1). ICER

is defined as the ratio of the incremental difference in total cost to the incremental difference in effectiveness when comparing alternatives. For example, if the question is whether to replace an existing treatment or intervention with a new one which is more effective but also more costly, then information about the additional recourses spent to achieve additional benefit is of importance for a decision-maker.

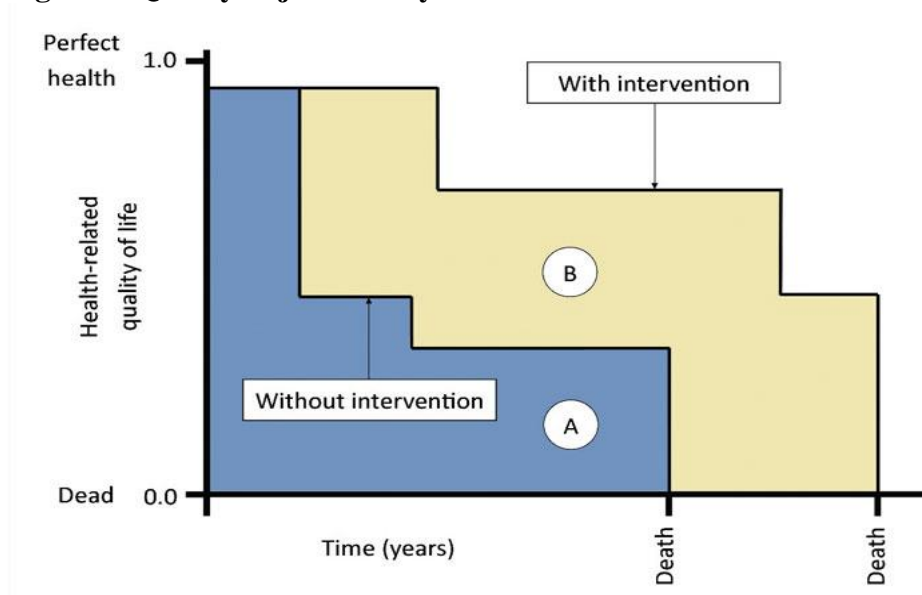
Box 1. Definition of the incremental cost-effectiveness ratio (ICER)

$\frac{[\text{Cost (B)} - \text{Cost (A)}]}{[\text{Effect (B)} - \text{Effect (A)}]}$	$\frac{\text{Difference in Cost}}{\text{Difference in Effect}}$
<p>Where B is more effective and more costly than A. (If B is more effective and less costly than A, it dominates A and the ICER is not calculated.)</p>	

ICER can be viewed as the incremental cost of producing extra health benefits from one alternative compared with the next most effective alternative intervention. For example, to determine cost-effectiveness, the ICER is a useful tool to help health planners take decisions on screening programmes when working within budgetary constraints; for example, they may be interested in maximizing the number of cases detected and knowing the incremental cost per case detected would therefore be relevant. However, “life years gained” might be a better outcome measure to use in a CEA of cancer screening programmes where the aim is to prevent morbidity and reduce mortality.

A *cost-utility analysis* (CUA) enables comparisons across different disease areas of costs related to a generic outcome (i.e. multidimensional consequences) (48). A common utility index that weighs the consequences of survival and quality of life is the quality of life year (QALY), a measure of disease burden including both the quality and the quantity of life lived (50). QALYs are calculated by multiplying number of life years gained by a utility value representing the health status of the individual. Value of utility ranges from 0 (i.e. dead) to 1 (i.e. perfect health) (see Figure 4). Rating scale, standard gamble or time-trade-off are used to measure utility values. The EuroQol five dimensions questionnaire (EQ-5D) is the most commonly used rating scale (50).

Figure 4. Quality-adjusted life years



“The area beneath the “without intervention” curve (area A) represents the number of QALYs associated with the control group. The area beneath the “with intervention” curve (area A plus area B) represents the number of QALYs associated with the intervention group. Area B represents the QALY gain associated with the intervention.”[Adapted from www.acnr.uk]

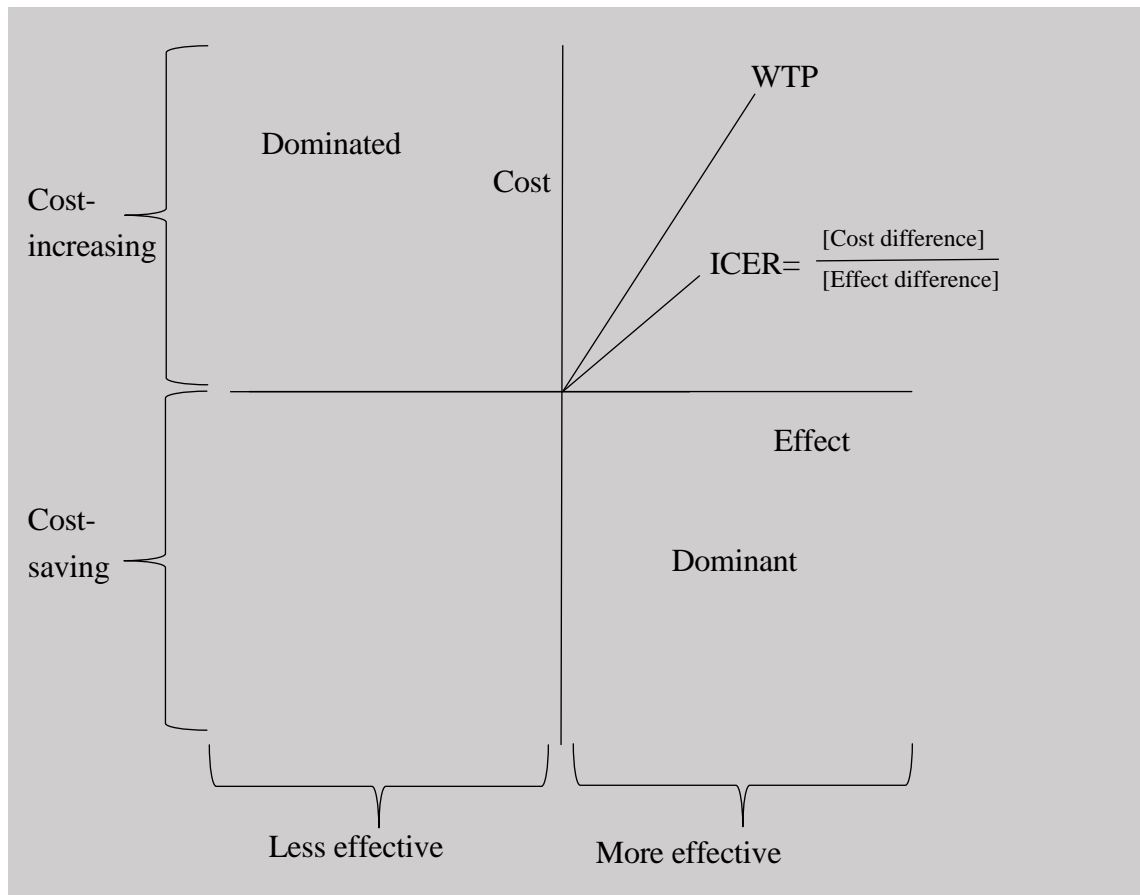
Cost-benefit analysis (CBA) expresses both cost and outcomes in monetary terms. A potential use is for comparing investments in the healthcare sector with investments in other sectors (e.g. road safety or education). The benefits are preferably measures by the willingness to pay (WTP). When value of the total benefit outcomes from a health care programme exceed the values of the total costs it is considered “good value for money”(48).

2.2.2 Decision rules of cost-effectiveness analysis

The cost-effectiveness plane (CE plane) forms the basis of several key studies presented in medical decision-making literature. It is an important tool used in cost-effectiveness analysis, and applied widely in the healthcare industry. The CE plane aims to illustrate differences in costs and effects between different chosen strategies (e.g. medical or no medical interventions, treatments, or combination of interventions and treatments). To make informed decisions regarding allocation of scarce resources, the CE plane visually presents the relative value of strategies, and informs its viewer to evaluate multiple strategies. Four different groups of results can occur when comparing two alternative interventions, as can be illustrated in a cost-effectiveness plane (Figure 5). With a reference strategy placed at the graphs, a cost-effectiveness analysis (CEA) can plot the incremental costs (y-axis) and effects (x-axis) of two alternative strategies, relative to each other. The area above the horizontal is cost-increasing, and to the right of the vertical, more effective with improved health. When a

new strategy is more effective and increases costs, an incremental cost-effectiveness ratio (ICER) is calculated.

Figure 5. The cost-effectiveness plane (CE-plane)



With a reference strategy placed at the graphs, a cost-effectiveness analysis (CEA) can plot the incremental costs (y-axis) and effects (x-axis) of two alternative strategies, relative to each other. When a new strategy is more effective and increases costs, an incremental cost-effectiveness ratio (ICER) is calculated.[Adapted from Drummond (46).]

The ICER should be valued by the decision-maker. An optimal choice depend on the willingness-to pay (WTP) for an additional unit of effect. If there is a defined WTP, choice of strategy depend on if the calculated ICER is below this threshold value. However, to determine which healthcare programme that is cost-effective, we need to determine how much society is willing to pay for a QALY (or for another effectiveness measure used in the CEA). Without information about this price per unit of health gain, a CEA provides no information on whether or not to implement a programme. This implies that the cost per QALY gained must be below a threshold value that reflects how much society is willing to spend to gain one QALY. The commonly used threshold value for cost-effectiveness usually ranges between USD 50,000 and USD 100, 000. Studies that estimate the social value of a QALY derived from estimates of the value of a statistical life (VSL) usually suggest even higher values (51, 52). In developing countries, the WHO Commission on Macroeconomics and Health suggests that interventions with an ICER costing less than three times the gross domestic product (GDP) per capita represent good value for money spent to eliminate each disability-adjusted life year (DALY) (53). Another way for national

governments to set threshold values is to base them on previous reimbursement decisions and guidelines (54).

2.2.3 Data for health economic evaluations

Costs are assessed in the same way for all types of health economic evaluations. First, identify the relevant resources used, regardless of whether they can be measured. Second, quantify the resources in physical units (i.e., number of clinic visits, hospital days, medical procedures, tests, etc.). Third, set a value for the resources used at their opportunity costs; for example, use the gross wage rate to value the time of patients or professionals. Recommended alternatives include the “micro costing” approach (although the need for accuracy in calculating costs must be weighed against the expense of collecting the necessary information), or the “macro costing” approach where costs are based on aggregate measures of resource use (i.e., a whole procedure for a medical event).

Perspective

The choice of perspective (e.g. patient, individual, employer, hospital, government, insurance company, private agency, and society) for the economic evaluation determines which costs to include in the analysis. To inform efficient allocation of health care resources, economic evaluations should be based on a societal perspective (55). A societal perspective implies not only that the costs that refer to the health care system should be included but also costs of informal care, loss of production, and costs of added years of life. If the economic evaluation is based on a restricted perspective (e.g. a health care perspective) this would not necessary lead to an efficient use of resources from a societal perspective. Moreover, diseases (e.g. cervical cancer) have a broad impact on a range of personal dimensions (e.g., patient health, quality of life, ability to work, social and sexual relations, and income). Furthermore, a narrow perspective makes comparing results difficult due to differences in health care from one country to the next (46).

Discounting

Often, economical analyses cover a long time period and costs and health effects do often not occur at the same time. For direct comparison treatments(s)/intervention(s) in different time periods, discounting should be made. Discounting is not a correction of inflation, instead it reflects time preference and the wish to have benefits earlier rather than later, and the returns that could have been gained if health recourses were invested somewhere else. Although, different opinions exist on whether both costs and effects should be discounted and whether health effects should be discounted using a lower rate, the usual recommendation is that costs and health effects in the base case analysis are discounted at the same rate. In a sensitivity analysis a lower discount rate for health effects should be used. Usually costs and health

effects are discounted with the same rate (3% or 5%) and in a complementary analysis health effects are discounted at 0% (46).

Future cost (costs of added years of life)

The most common practice in cost-effectiveness analysis is to include future medical costs only for “related” diseases and excluding future medical costs for “unrelated” diseases and future non-medical costs. However, Meltzer (1997) that bases the cost-effectiveness analysis on the theory of welfare economics concludes that all future costs (medical and non-medical) should be included in a cost-effectiveness analysis. An intervention that increases survival implies changes in medical and non-medical consumption and may also result in changes in production that should be taken into account in a cost-effectiveness analysis from a societal perspective. Thus, to reflect the societal cost perspective the difference between total consumption (medical and non-medical) and production of added years of life should be included in a cost-effectiveness analysis (56). The difference between total consumption and production in life-years gained depends on the age. Individuals who are not part of the labor force consume more resources than they produce, while those in the labor force produce more than they consume. One consequence of not including costs of added years of life is that interventions are favored that extend life over those that improve quality of life for the elderly, while the opposite is the case for younger (56-59).

Resource type and valuation

International comparability between economic analyses may contribute to rational decision-making in healthcare policy. Although estimates should preferably be comparable between countries, outcome results may be confounded by variations in methodology, data sources, valuation of production losses, and social security arrangements (60). When considering costs, they are divided into *direct* and *indirect* costs (46). *Direct costs* include direct medical and direct non-medical costs. Direct medical costs include inpatient (hospital) and outpatient care (e.g. visit to a medical professional at an outpatient clinic), medical procedures, tests, medical devices and home health services. Direct non-medical costs are unrelated to health care and include costs for travel, transportation, adaptation, investments, assistance, and unpaid care by family, friends or relatives. *Indirect costs* relate to productivity loss to society due to healthcare programs or illnesses (e.g. sick leave, reduced productivity, early retirement). Individuals who are not part of the labor force have no indirect costs. Estimates of indirect costs often influence the outcome of economic evaluations. Another consideration is the leisure time lost by patients due to use of health care services (i.e. unpaid activities) and valuation of these (61). *Intangible costs* include such consequences (e.g., pain, psychological suffering, and change in social sexual functioning or sexual functioning caused by disease) that are difficult to measure and value; they are rarely included in economic evaluation, but are sometimes reflected in the denominator of the ICER.

Important practices when estimating costs include identifying relevant resources, quantifying these resources and assessing the costs of the quantified resources. Economic theory states that a resource should be priced based on its opportunity costs (i.e., the value of the benefits

forgone when the resource is not available as the best alternative for use) (46), though market price, which is often available, is more often used. When assessing the value of informal care (i.e., care provided by family, relatives or friends), income lost is often used and opportunity cost can be estimated using the gross wage rate of caregivers (48), though informal care is often provided during leisure time. The opportunity cost of leisure time has been suggested to be valued at null, or based on average earnings, overtime earnings or a rate reflecting the take home pay. Alternatively, informal care can be valued using the replacement cost method (i.e., at market value for caregivers) (55, 62). Another approach used to value changes in productivity (i.e., indirect costs) is the human-capital approach, which estimates the value of lost production for those employed based on gross earnings (63). However, this approach has been criticized since it does not take into account replacement of the absent worker, which reduces productivity loss. Therefore, the friction-cost method, which only considers loss of production due to the absent employee, should be used in assessments until the initial level of productivity can be restored (64). However, criticism has been aimed at this approach because it is based on assumptions. A more recent approach holds that the value of absence may affect team productivity and give rise to higher production loss (65).

2.2.4 Cost of illness

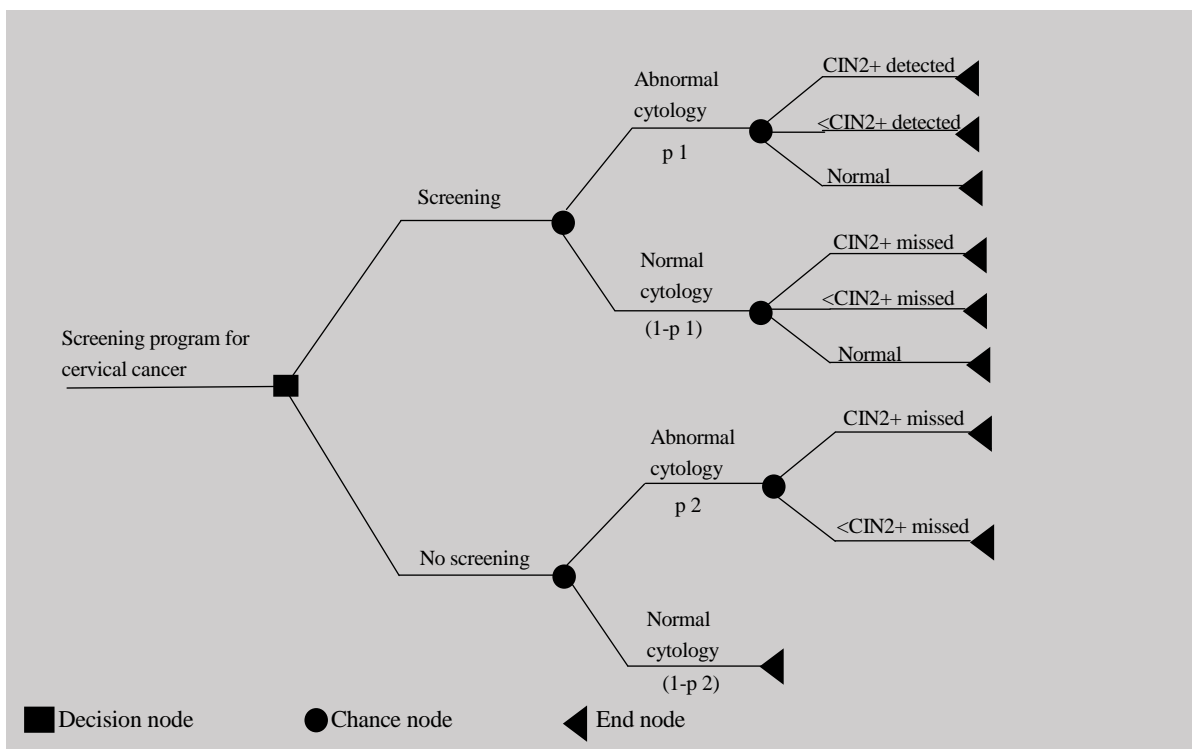
A cost-of-illness study is a descriptive type of analysis which estimates disease-specific costs, and provides information on the maximum potential savings that could be done if a disease were to be eradicated. Cost-of-illness studies are most commonly based on a top-down or bottom-up approach (66). A top-down approach considers the total national costs for a disease, divided among different types of disease after diagnosis of the principal disease. When using a bottom-up approach, data are collected from the study target population and estimates are extrapolated to make them representative for an entire population by using national prevalence estimates. One benefit of the top-down approach is that extrapolation is unnecessary, thereby avoiding the risk of duplication of costs. The disadvantage is that diagnoses may not be reported, or may be misclassified, which leads to missing costs in the national registries. However, costs for social services, unpaid help and net cash outlays are not taken into consideration, though mortality and disability pension are recorded by main diagnosis in the national registries. Statistics regarding short-term sick leave and unpaid time off work usually are not recorded. Cost-of-illness studies are performed using either the prevalence or incidence method. The prevalence-based approach considers those costs incurred over a given time period, usually one year, without regard for date of onset. The incidence-based approach considers the costs for a disease that develops for the first time in a given time period. Future costs and production losses are estimated over a life time and calculated in current values. Incidence-based studies are suitable for evaluating preventive measures when calculating the economic benefits of reducing the number of new cases (67). If cost control is the major concern, the prevalence-based approach is preferable, since the main resources used and the indirect costs are identified and can be used in the effort to achieve savings.

2.2.5 Decision-analytic modeling

When there is uncertainty about a decision for which information is available to serve as a base, decision-analytic modeling is commonly used. The purpose of modeling is to: (1) simplify a complex situation by isolating critical study aspects; (2) integrate data from various sources (i.e., economic, clinical or epidemiological data) and (3) project simulated outcomes from alternative actions beyond the time frame of the data in order to understand long-term implications (63, 68). One approach is the *within trial* analysis using patient-level information where analysis and data collection concerning costs and effects are carried out simultaneously with the clinical trial. However, unforeseen consequences may arise following the clinical trial period; in health economic evaluation, all relevant costs and effects need to be considered, regardless of occurrence in time. Furthermore, the clinical trial target population is never fully representative of the actual target population. Therefore, *decision-analytic simulation modeling* can be used when estimating the cost-effectiveness of an intervention. Various techniques include: *decision-tree models*, *Markov cohort models*, *individual-based simulation models* and *discrete event simulation (DES) models*. A *decision tree model* calculates costs and health outcome (e.g., probabilities and payoffs) between alternative interventions and is suitable for short-term analyses or when outcomes are limited. See further example in Figure 6 below.

Markov models are discrete health state-transition models based on continuous risk over time and are commonly used for interventions characterized by a recurrence of events, such as screening programs for a specific disease (e.g., cervical cancer or colorectal cancer)(68). It is important to keep in mind that no memory assumption is made and that future events depend only on the current state (69). When the model's probabilities, costs and effects need to be changed following an event over time, an *individual-based simulation model* is appropriate. The possibility of tracking the history of the model pathway can be used to provide information when applying probabilities, costs and effects in the simulation model. One type of individual simulation model is the *discrete event simulation (DES) model* that focuses on events rather than health states, as in the Markov model simulation. In a DES model, individuals are followed over time and at discrete points in time, events occur according to a *queue of events*; an individual can be in multiple activities at the same time. DES is also particularly well-suited to diseases such as cancer, where the key factor in the disease epidemiology is the time when an event occurs (63). For example, HPV vaccination should be given prior to sexual debut (girls and boys at age 10-12) to have the best possible effect and avoid cervical cancer later in life.

Figure 6. Decision tree



The cost-effectiveness of treatment/intervention compared with no treatment/intervention would be estimated by comparing the two strategies. In this example of a decision tree, a decision is made to attend or not to attend the screening program that reduces the risk of CIN2+ and consequently cervical cancer (decision node). In both cases, women can have CIN, but the probability (chance node) in the intervention group (p_1) is lower than in the no screening group (p_2). Consequently, cost of screening for cervical cancer is lower in the intervention group since less women develop cervical cancer based on the assumption that they are treated in the same way in both groups when cervical cancer are detected.

Uncertainty

Uncertainty always occurs in model-based cost-effectiveness analyses and can be categorized as: *methodological*, *modeling*, *transferability*, *generalizability* and *parameter uncertainty* (70). *Methodological uncertainty* occurs when comparing outcomes from studies that are based on different methodology and is often handled using sensitivity analysis and a reference case. *Modeling uncertainty* is related to the development of the model and dealt with using sensitivity analysis or changing the model structure. When applying results from one model to other settings, *transferability and generalizability uncertainty* occurs. Most commonly discussed is *parameter uncertainty*, which refers to the uncertainty concerning the input data of the model and is related to the limitations of the data used in the model. Here too, sensitivity analysis is an important tool to validate the results of the cost-effectiveness analysis. A one-way sensitivity analysis or a probabilistic analysis may be used to address uncertainty by varying one or several parameters in the model within a given range and by doing Monte Carlo simulation.

2.3 KEY FACTORS AFFECTING THE COST-EFFECTIVENESS OF CERVICAL CANCER SCREENING PROGRAMS

To present an overview of past and recent health economic studies of cervical cancer and key factors that affect the cost-effectiveness of screening programs, a literature search was conducted using PubMed, MedLine and the Health Economic Evaluation Database (HEED) to find relevant publications. This chapter outlines key factors that have impact on the cost-effectiveness of cervical cancer screening programs including burden of cervical dysplasia and cervical cancer, morbidity and mortality and different types of screening tests, treatments and adverse events. A discussion about the potential effect of HPV vaccine on screening, as well as issues concerning epidemiology and cost-effectiveness are included. Other factors affecting the cost-effectiveness of a screening program is access to screening, population coverage, knowledge and acceptability among the population which is presented in next chapter; 2.4“Barriers to and facilitators of compliance with cervical cancer screening”.

2.3.1 Disease burden

Worldwide, cervical cancer is the third most common cancer among women, only exceeded by breast and colorectal cancer, with an estimated 530 000 new cases and 275 000 cancer deaths in 2008 (71). More than 85% of the global burden occurs in developing countries where no prevention program is offered, including organized screening programs, vaccination or adequate treatment. The highest risk is found in Eastern or Western Africa, where age-standardized rates are above 30/100 000, while the lowest risk is found in Western Asia, North America and Australia, where age-standardized rates are below 6/100 000.

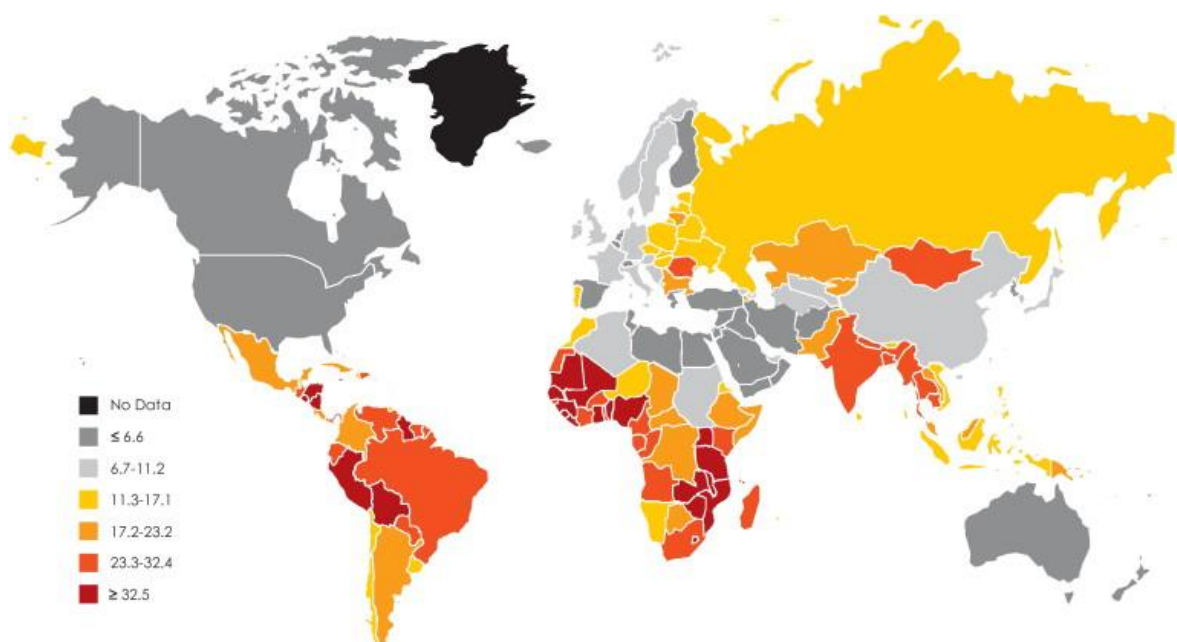


Figure 7. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Worldwide cervical cancer, map presenting estimated age-standardized (world standards) incidence per 100 000 in 2008 (all ages).* [Adapted from GLOBOCAN 2008(72)].

Criteria for implementing a screening program

In 1968 the World Health Organization established a list of general criteria for screening for any disease (73):

Box 2. General criteria for implementing screening

- (1) The condition should be an important health problem.
- (2) There should be accepted treatments for patients with recognized disease.
- (3) Facilities for diagnosis and treatment should be available.
- (4) There should be a recognizable latent or early symptomatic stage.
- (5) There should be a suitable test or examination.
- (6) The test should be accepted by the population.
- (7) The natural history of the condition, including from latent to declared disease, should be adequately understood.
- (8) There should be an agreed policy on what patients to treat.
- (9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- (10) Case-finding should be a continuous process and not a “once and for all” project.

In countries with organized screening programs, incidence and mortality have been dramatically reduced due to the ability to identify precancerous lesions and to treat early stages of cervical cancer (74, 75). In Sweden, there has been a 67% reduction in the incidence of cervical cancer, although this trend has stagnated somewhat in recent years (76). According to 2012 statistics from the Swedish National Board of Health and Welfare, the decline in incidence has gone from 20 cervical cancer cases per 100 000 women in 1965 to around 7/100 000 in the late 1990s. In the 35-39 year age group, there was a 66% reduction in incidence from 46.0 to 15.5 per 100 000 women from 1958 and 2004. In the 70-74 year age group, there was a 42% reduction (27.0-11.4 per 100 000 women) during the same period. According to the Swedish Cause of Death Register, the age-standardized mortality rate was 7.7 per 100 000 women 1959 and 2.8 2004 (77). Despite the decline in the incidence of squamous cell cervical carcinoma over the same time period following the introduction of organized Pap smear screening, the incidence of adenocarcinoma increased annually in Europe by 0.5 to >3%, especially among women below age 40 (78-82). The Pap smear has proven to be less effective in detecting ADC, while more effective in detecting SCC, especially among women <40 years (83, 84). According to registry-based reports, 20% of Swedish women do not participate in cervical cancer screening (85) and it is recognized that they are at greater risk of developing cervical cancer (1, 37, 74, 85, 86).

2.3.2 Screening for cervical cancer

Today, it is known that persistent infection with oncogenic human papillomavirus (HPV) precedes cellular neoplasia (8). Knowledge about the natural history of the disease has led to the development of cervical cancer prevention methods, including screening with cytology and, more recently, HPV testing and HPV vaccination. Until recently, no randomized-

controlled trials (RCTs) have shown that screening, including treatment of CIN, reduces cervical cancer incidence and mortality (87). The effects of cervical cancer screening have been assessed using studies of observational that have shown a rapid decline in the incidence of cervical cancer following implementation of organized screening programs. A 2009 RCT from India that compared conventional cytology screening using either Pap smear or HPV testing with no offered screening confirmed that screening with HPV tests was an effective prevention method for reducing both the incidence and mortality of cervical cancer (88). Cervical cancer screening programs vary by country and setting (89).

Organized screening program in Sweden

Sweden introduced organized screening in the early 1960s and the program had become common practice by 1974. The screening program resulted in a significant reduction in the incidence of SCC, while the impact on incidence of ADC was more modest (82). A comparison of the screened and unscreened populations showed a difference in the cancer detection rate in the early stages (55% vs. 17%) and the percentage of advanced stages FIGO III and FIGO IV declined from 29% to 21% and mortality also declined due to the early detection of CIN and treatment of precancerous lesions, as well as early stage detection (37). In Sweden, all women aged 23-49 are offered cytology testing (either Pap smear or Liquid-based cytology (LBC) at a local outpatient clinic every three years and women aged 50-60 are called every five years. Abnormalities are followed up immediately using colposcopy with biopsy, as recommended by WHO guidelines (available at www.sfog.se). Today, several trials have shown that HPV testing is highly sensitive, but less specific (90). Also, large population-based randomized controlled trials have shown that primary HPV testing is more effective than conventional cytology in reducing both the incidence and mortality of cervical cancer (91). The risk of detecting CIN3 or cancer is lower 5 years after an HPV-negative test than 3 years after a negative Pap test; HPV DNA has a higher prospective negative predictive value (92). However, the optimal screening interval has yet to be determined (93). Because of these advantages, the Swedish screening program is currently transitioning from primary screening with Pap smears to primary screening with HPV testing. Consequently, existing screening protocols are being modified and new follow-up procedures for HPV-positive women are being developed in countries with organized screening.

Clinic-based screening

Pap smear

The WHO recommends Pap smear screening, first developed by Dr. Papanicolaou in 1941. Precancerous lesions develop in the TZ, from which a cytology sample is taken. Exfoliating cells are collected from the ectocervix by using a spatula. Exfoliating cells are collected by using a brush from the endocervix. The samples thereafter are directly smeared onto a glass slide and fixed in 95% ethyl alcohol to prevent air-drying. The glass slide is examined under a microscope. Adequate samples contain both metaplastic squamous cells and endocervical

cells. European guidelines recommend three methods for sampling (74). However, a combination of Cytobrush and spatula is preferred (94, 95). The Pap smear has limited sensitivity for histologically confirmed CIN2+ (50%-70%) (90, 96). A systematic review showed highly variable sensitivity ranging from 30%-87% with specificity ranging from 86%-100% (97). The overall low sensitivity can be improved with repeat testing 3 to 5 years later as part of the screening program. Pap smear is less protective against development of ADC than SCC. An Italian study found that the odds ratio for developing ADC among women who had undergone Pap testing within 3 years of the index date was 0.65 (95% confidence interval (CI) 0.26-1.64), while the corresponding figure for SCC was 0.15 (95% CI 0.07-0.31). The protective effect was shorter in duration for women under age 40 than for older women (83).

Liquid based cytology

Liquid-based cytology (LBC) was developed to improve the quality of conventional Pap smears and introduced in the 1990s. The collection method is the same as for Pap smears. The sample is immersed and rinsed in a vial containing collection fluid and then processed. Available tests are ThinPrep (Cytec Corp. Marlborough, MA, USA) and SurePath (BD, Franklin Lakes, NJ, USA). The ThinPrep method was approved by the United States Food and Drug Administration (US FDA) in 1996. Most importantly, LBC enables supplementary sampling of HPV DNA (e.g. HPV reflex testing), which increases the efficiency of cytology screening. Whether LBC is more accurate than the Pap smear remains to be seen. A study comparing Pap smears with LBC found that the ThinPrep method was somewhat more sensitive (66% vs. 47%). Similar results were found in a randomized controlled trial (RTC) (98). However, a meta-analysis showed that LBC and Pap smear had similar accuracy (99). In addition, a Swedish study found no significant difference in accuracy between LBC with HPV DNA testing (reflex method) and conventional Pap smear (100).

HPV-tests

Today, all HPV testing is based on detection of HPV nucleic acids, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), in clinical samples (101). One review assessed 125 commercially available HPV tests (102) and an increase in the number of tests is expected due to the wide range of clinical applications. HPV testing displays higher sensitivity than cytology testing, but lower specificity for detection of histologically confirmed CIN2+. The higher negative predictive value (NPV) of HPV testing provides additional assurance for HPV-negative women that they do not have any significant precancerous lesions. US FDA-approved tests include: Hybrid Capture 2 (HC2) (Digene Corporation, Gaithersburg, Maryland, USA), Cervista HPV HR (Hologic, WI, USA), Cervista HPV 16/18 (Hologic Inc., Bedford, MMMA, USA) and Cobas 4800 HPV test. Cobas was evaluated in the ATHENA study (Addressing THE Need for Advanced HPV Diagnostics study) (103). Only one RNA-based assay is available, the APRIMA HPV assay (formerly GenProb Inc., San Diego, CA, USA) (101). The Hybrid Capture 2 HPV DNA test

is the most frequently used HPV test worldwide. The HC2 detects 12 HR-HPV types (IARC-2009) and HPV68. It was FDA-approved in 2003 for triage of women with minor cytological abnormalities, as well as for triage in women over age 30, and has been shown to perform well clinically in international RCTs and cohort studies. Other HPV tests need to demonstrate similar clinical performance before being recommended for use in clinical studies (102).

The feasibility of HPV testing for use in primary screening has been subject to discussion mainly because of its low specificity when used as a single HPV test, especially among young women, where HPV testing leads to over-diagnosis of regressive CIN2 (104). One large review showed that this method was more sensitive than cytology for detecting CIN2+ (96.1% vs. 53.0%), but less specific (90.7% vs. 96.3%); specificity of both tests increased with age (105). However, cytology was substantially more sensitive among women over the age of 50 than among younger women (79.3% vs. 59.6%) (105). One study showed that women found to be HPV-negative at baseline had a significantly higher NPV for progression to CIN3 or worse than women found to be cytology-negative at baseline (92). HPV testing in primary screening and cytology as triage showed higher sensitivity in detecting CIN3 or worse than primary cytology alone (106). Apart from the feasibility of HPV testing for primary screening and especially among women over age 30, HPV testing can also be considered useful for triage to identify those women with minor cytological abnormalities who are truly at risk of progressing to HSIL and need further follow-up with gynecological examination. Another application involves follow-up of women previously treated for CIN to predict further risk of developing cervical cancer (107, 108).

Home-based screening

Self-sampling combined with HR-HPV testing is a rather new approach to screening. HPV testing is performed in the privacy of the home as a feasible alternative for non-participants in clinic-based screening programs, hard-to-reach women and women reluctant to undergo vaginal examination (109, 110). Overall, it could potentially increase the overall participation rate of organized screening (111). A response rate of 40% was found in a Swedish study of almost 3000 women aged 30-58 who had not attended screening for ≥ 6 years. They were offered self-sampling at home (Qvintip) and asked to send the vaginal fluid sample to a laboratory for hr HPV analysis (HC2) (110). The study found a high prevalence of HR-HPV, ranging from 11.1% in women aged 30-39 to 2.9% in women \geq age 50. Histological CIN2+ was detected in approximately 43% of the women with persistent HPV infection (2.0% of the total number of responders). By comparison, the sensitivity of a single Pap smear for detection of CIN2+ was 52.6%. A study was conducted on post-menopausal women (age 55-76) who were offered both HR HPV testing and conventional Pap smear as part of the gynecological screening program from 2008-2010. The results found HR-HPV in 6.2% (95% CI 5.2-7.3%) of these women, 22% (95% CI 14-32%) of whom had CIN2+; most of the CIN2+ lesions in post-menopausal women were not detected by a single Pap smear (112).

A meta-analysis of almost 40 studies with data from approximately 150 000 women showed that average sensitivity for detection of CIN2 was 76% (95% CI 69%-82%) and for CIN3 84% (95% CI 72%-92%), while specificity for CIN2+ was 86% (95% CI 83%-89%) and for CIN3+ 87% (95% CI 84-90) (113). Samples taken by a clinician showed overall higher accuracy (pooled sensitivity and specificity) than self-sampling performed by the women themselves. Self-sampling combined with HPV testing using signal-based assays was both less sensitive and less specific than sampling by a clinician. However, some PCR-based (polymerase chain reaction, a technology that selectively amplifies a target sequence of DNA) HPV tests showed similar sensitivity between samples collected by the women themselves and those taken by a clinician. Therefore, the meta-analysis concluded that organized screening programs that use signal-based assays (cell-based assays) should rely on samples collected by a clinician. However, some PCR-based HPV tests were considered after thorough pilot studies to assess feasibility. Study II, in present thesis, was modeled on data from a study examining HR-HPV among women aged 30-65, using PCR-based HPV tests. The women used a “Viba-brush (Rovers Medical Devices, B.V., Oss, the Netherlands)” to collect vaginal cells, which were then applied to an indicating “FTA™ Elute Micro Card (GE Healthcare, Chalfont St Giles, UK)”, and subsequently mailed for HPV analysis using an “RT-PCR capable of detecting HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59” (114-116). This study found HR-HPV in 6.6% of the women, 89% of whom performed follow-up examination on average 2.7 months after the initial test; 59% of these women were HR-HPV-positive in the follow-up test (114). Among the women with a positive initial HR HPV test, 23% were HR-HPV-positive (95% CI 18-30%), and 41% (95% CI 31-51%) of women who repeated the test almost 3 months later were HR-HPV-positive. Repeat HR HPV testing at short intervals increased specificity for detection of CIN2+ lesions from about 94.2% to 97.8%.

2.3.3 Follow up, treatment for CIN and adverse events

Colposcopy is used for follow-up of abnormal cytology to identify diseased tissue for sampling biopsies to provide histopathological confirmation of cytology results. Some studies have questioned the accuracy of colposcopically-directed punch biopsies. According to one meta-analysis the threshold for distinguishing between a normal cervix and LSIL, compared with HSIL and cancer, showed an average weighted sensitivity of 85% and average weighted specificity of 69% (117). One important factor for high sensitivity was a highly skilled colposcopist taking random and multiple biopsies, which increased detection of CIN2+ (118, 119). The policy of continued monitoring of women with CIN1 was developed from the TOMBOLA trial to reduce potential over-treatment of regressive CIN1-2 (119).

Treatment for CIN2+ is recommended by most guidelines in countries with organized screening. Women under age 40 diagnosed with CIN 1 are usually invited for follow-up 1 year later, while treatment is recommended for women older than 40. Alternatives of management and treatment for CIN include ablative techniques such as cold knife cone

biopsy, loop electrosurgical excision procedure (LEEP), electrofulguration, laser conization, laser ablation, cryotherapy and hysterectomy. There were no significant differences in treatment outcome according to a recent published review (120) .

Literature reviews have shown an increased risk of cervical cancer after treatment, which mandates more frequent follow-up (121, 122). The incidence of cervical cancer was higher among treated women than among untreated women (37 vs 6 cervical cancer cases)(123). According to a 2014 study by Stander et al., women with CIN3 were at increased risk of mortality (standardized mortality ratio 2.35, 95% confidence interval 2.11 to 2.61) from ICC or vaginal cancer, compared with women in the general population (122) . Their study also showed a higher incidence of cancer among those treated with cryotherapy. LEEP is recommended in Sweden and is the most commonly used treatment in Swedish health care. Moreover, women treated for CIN are at increased risk of adverse birth outcomes; cold-knife conization has been specifically associated with increased perinatal mortality, preterm delivery, extreme preterm delivery and low birth weight (124, 125).

2.3.4 Human Papillomavirus vaccines

Two prophylactic HPV vaccines are available for cervical cancer prevention: Gardasil® (quadrivalent vaccine targeted at HPV types 6, 11, 16 and 18) developed by Merck (Whitehouse Station, New Jersey, USA) and Cervarix® (bivalent vaccine targeting HPV 16 and 18), developed by GlaxoSmithKline (Brentford, Middlesex, UK), both of which target HPV 16 and 18, which account for around 70% of cervical cancers worldwide. Two studies, FUTURE I and FUTURE II, evaluated Gardasil®, while PARTICIA and the Costa Rica HPV Vaccine Trial (CVT) evaluated Cervarix®. The studies found that both vaccines show high and similar efficacy. Phase III trials are currently underway. A nine-valent vaccine targeting HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 was recently developed and is expected to prevent 90% of cases of invasive cervical cancer (126). Three systematic reviews of the quadrivalent and bivalent HPV vaccines presented a significantly lower risk of CIN2+ in women that was vaccinated compared with unvaccinated women (127-129). The vaccines have no therapeutic effect on established HPV infections or on CIN. However, the rate of reduction varied according to whether women had a history of exposure to HPV 16 or HPV 18. However, the vaccine would be effective in 90% of HPV naïve women. A recent study found that the HPV vaccine had high efficacy against CIN2+ in women with serological evidence of past infection with HPV type 16 or 18, but without active infection at the time of vaccination, suggesting that these women would also benefit from HPV vaccination (130). Both HPV vaccines are associated with cross-protection against HPV types not included in the vaccine (HPV 31 for Gardasil and HPV 31, 33, 52, 45 and 51 for Cervarix). Studies have shown that Gardasil has been proven efficacious in women aged 24-45 and men aged 16-26 for incident HPV infections, genital warts, anal intraepithelial neoplasia and for CIN (solely in women). However, concerns have arisen that an empty ecological niche could be developed for other HPV types if HPV 16 and HPV 18 are eradicated, but as yet there is no proof of this. Safety evaluations following the introduction of the vaccines have shown that they are very safe. One study compared the incidence of 53 serious events in HPV-vaccinated girls with non-vaccinated girls in Sweden and Denmark after the introduction of the vaccine, and found no

evidence supporting associations between exposure to quadrivalent HPV vaccine and autoimmune, neurological or venous thromboembolic adverse events (131). High coverage was first achieved in Australia and evaluations have shown a reduction in genital warts both within the vaccinated group of women and among men, suggesting herd immunity (132). Also, in Sweden reduction of genital warts has been demonstrated after 2 doses of vaccine (126). In Sweden, HPV vaccination has been offered to girls aged 10 within the framework of the organized school vaccination program. Some counties in Sweden have offered catch-up vaccination to girls age 18-26. Duration of vaccine efficacy is a key parameter. However, studies to confirm a reduction in the number of cervical cancer cases are still lacking. Thus the HPV vaccines suggest sustained immunity and could potentially change the screening approach.

2.3.5 A summary of cost-effectiveness studies on screening for cervical cancer and vaccination

Screening

Cost-effectiveness studies prior to 2000 focused on evaluating available screening technologies such as liquid based cytology (LBC) and testing with HPV for primary screening alone and for follow-up of ASCUS and LSIL/CIN1 compared with conventional Pap smear. A switch from Pap smear to LBC in Sweden has been proposed and has been found to be cost-effective internationally. However, since the previously cited study found no statistically significant difference between LBC and Pap smear for detection of HSIL/CIN2+ (133) or in cost-effectiveness, comparisons should be regarded with caution. Reviews of cost-effectiveness analysis of screening with HPV tests in addition to conventional cytology concluded that screening for HPV is potentially-cost-effective, provided that the time interval between screenings is adjusted for women above 30 or 35 years (134). HPV testing combined with cytology at 2-3 year intervals for women above age 30 or 35 years with ASCUS has proven to be less costly and may potentially increase life expectancy compared with conventional cytology alone (135). Annual cytology-based screening also proved to be more costly and led to more follow-up procedures, with little gain in life expectancy. Furthermore, studies suggest that HPV DNA testing followed by cytology to triage women who are HPV-positive may be a cost-effective screening strategy for older women (136, 137). Recent clinical trials confirming the high sensitivity and specificity of HPV testing in primary screening using repeat HPV self-sampling at home at short intervals (112, 114) and more recent cost-effectiveness studies showing that clinic-based HPV testing in primary screening and Pap smear triage of ASCUS-LSIL (138, 139) could be effective and/or cost-effective indicate a role for HPV testing in the preventive program for cervical cancer in Sweden. However, there are too few cost-effectiveness studies on HPV self-sampling performed at home compared with clinic-based cytology screening. Nevertheless, one study built on data from a single clinical trial confirmed that HPV self-sampling may potentially be a cost-effective option (140). Since the effectiveness of a screening program relies on participation

and compliance, acceptance among the population must be high towards self-sampling performed by the women themselves. The aforementioned study found that over half (60%) of the women in the study group preferred a self-sampling performed at home as it were easier to perform at home and created less of an inconvenience for the women, provided it is as effective as clinic-based testing. Organized screening programs are both highly time consuming and resource intensive. In Sweden, annual direct disease-related screening costs are covered by the publicly funded Swedish national healthcare service. Both attendance and non-attendance within the organized screening program will inevitably generate as yet unknown and unaccounted for future costs for society. The availability of HPV testing both in the clinic and at home raises the question of whether to implement HPV testing in primary screening for detection of high-risk patients in the general female population. However, cost-effectiveness studies are still needed. We lack published cost-effectiveness studies on home-screening for HPV compared with clinic-based cytology screening. Furthermore, estimates of disease-related direct and indirect costs are needed and should be included in economic evaluations according to health economic evaluation recommendations (55).

Vaccination in combination with screening

Much of the epidemiology and the natural history of infections with HPV, cervical dysplasia and cervical cancers are still unknown and in need of further research. Both the effectiveness and cost-effectiveness of HPV vaccines will depend on the organized screening program, the HPV vaccination strategy and the overall costs of the HPV vaccination program. Previous cost-effectiveness models for HPV vaccine have examined the effects of preventing HPV infection on the incidence and mortality rate of cervical cancer. *Cohort models* and *dynamic transition models* have been used to evaluate the effectiveness of HPV vaccine. A third category is the *hybrid model*, which uses a combined approach. The cohort model simulates the natural history of HPV and cervical cancer of a cohort over its expected life time. Cohort models (health-state transmission models) are generally linear and probabilistic, while dynamic models are non-linear and deterministic since they track populations over time and take birth and death into account. Dynamic models take the rate of HPV infection into account. The rate of HPV infection depends on the sexual behavior of the population and the distribution of HPV infection. The strength of the dynamic model is that the herd immunity (immunity occurring when vaccination is performed on a significant proportion of a population, which also has an effect on those who have not developed immunity) resulting from the HPV vaccination program can be evaluated by methods such as exploring the effect of vaccinating boys, or patterns of sexual activity at onset of vaccination (141). Dynamic models have examined the reduction in incidence of HPV infection in relation to a vaccinated population. A study assumed that 80% of women were vaccinated before onset of sexual debut and projected a 92% reduction of the incidence of infection with HPV among young women aged 15-19 (142).

Limitations in dynamic models relate to the simplification of the complex and as yet highly undefined natural history of HPV infection, due to constraints in the modeling technique. This could lead to underestimations of the benefits of screening when evaluating screening alternatives with complex triage algorithms (142). To handle such limitations, hybrid models can be used. Hybrid models can project HPV incidence for various vaccination program scenarios and allow the outcome to be put into a cohort model to further examine the effects of herd immunity on reducing cervical cancer incidence and disease related mortality, while simultaneously taking into account the complexity of triage algorithms.

Cost-effectiveness of screening and vaccination

Taking into account various settings, with and without screening, for use in various model structures such as cohort, dynamic or hybrid models, the reviews of such cost-effectiveness models suggest that HPV vaccine programs could potentially reduce the incidence of CIN, cervical cancer and mortality (143-145). Suggestions are therefore based on models that project outcomes with assumptions concerning the lifelong duration of vaccine efficacy and high coverage. Such assumptions may need to be modified to simulate more real-life settings with lower coverage (144). Therefore, model-projected results must be updated as vaccine programs are implemented in different settings and as evidence concerning duration and coverage accumulates. In the aforementioned reviews, vaccine dose price affects the cost-effectiveness of adding vaccination to the screening program. In countries with no organized screening, potentially HPV vaccination could be a cost-effective prevention method compared with no prevention (146). Also, as can be expected based on vaccination trials, solely administering HPV vaccinations to young girls prior to sexual debut could potentially be a cost-effective option compared with HPV vaccination for girls, boys and catch-up vaccinations. However, vaccinating boys also provides a direct benefit by reducing HPV-related cancers and protecting against genital warts in men. The indirect benefits of increased herd immunity include protection of unvaccinated men and women in general, as well as men who have sex with men. HPV-related diseases are less common among men than in females and men benefit from vaccinated women through herd immunity. If coverage is less than 50% including men in the HPV vaccination program is potentially cost-effective (132). The question of whether to include men in the vaccination program is ongoing. In Australia, the government approved vaccination of men in 2012 and commenced in 2013. One model study of a heterosexual population projected near elimination of genital warts in both men and women (147). However, as more empirical data on herd immunity, vaccine coverage and vaccine duration become available, models will need to be updated.

Screening in the era of HPV vaccines

A recent review concluded that existing cervical cancer screening techniques are effective, although organized screening programs should consider implementing HPV testing and further process developments for alternative screening methods (148). The question of whether and how screening methods should change when combined with HPV vaccine programs is complex and depends on a number of key issues, some of which are still unknown. Such key issues include performance of HPV testing, reduction in the rate of CIN and cervical cancer, and whether HPV vaccination will alter participation and compliance with the screening protocol. One potential future approach for vaccinated women is HPV testing in primary screening with cytology triage, while postponing onset of screening to a later age and employing less frequent screening intervals over the lifetime of these women (137). Given the potential for cervical cancer to become a low-incidence disease in the future, the current screening policy needs to be reconsidered.

2.4 BARRIERS TO AND FACILIATORS OF COMPLIANCE WITH CERVICAL CANCER SCREENING

For a cervical cancer screening program to be effective, screening procedures must be acceptable to the population (the sixth criteria for implementing a screening program according to the WHO) and the screening schedule must be closely followed. Compliance with current screening policy using conventional cytology and factors that affect compliance have been widely evaluated in the past. However, a change from conventional cytology screening to HPV testing in primary screening, based on previous evidence, suggests that time intervals between screenings could be longer and triage testing for HPV-positive women should be implemented. The implementation of HPV testing could potentially alter public perception of cervical cancer by clarifying the etiologic role of a sexually transmitted virus. This may affect coverage or participation, as well as compliance with screening protocols. Such a change could possibly have a different effect on women of lower socioeconomic status, which needs to be addressed. A literature review was therefore conducted on PubMed to identify relevant publications containing information on knowledge of and attitudes toward HPV, HPV screening, screening attendance and socioeconomic status, coverage, as well as participation and compliance. This chapter summarizes the relevant findings from these studies.

2.4.1 Knowledge of HPV and related diseases

Overall, women with lower socioeconomic status are less knowledgeable about HPV, its relationship to cervical cancer and its risks. Interesting studies performed just before the vaccines were released examined awareness and knowledge of HPV as well as barriers to cervical cancer screening. One international study investigated the level of knowledge and barriers to cervical cancer screening among female university students in Malaysia and concluded that important correlates of knowledge of cervical cancer were age, marital status, ethnicity, family income level and university faculty attitudes ($p=0.003$; $p=0.001$; $p=0.002$; $p=0.002$; $p=0.001$ and $p=0.002$; respectively) (149). In this study, the most commonly known and reported risk factor for cervical cancer was having more than one sex partner (77.5%), while the least commonly known risk factor concerned the relationship between HPV and cervical cancer (51.2%). In a UK study, face-to-face interviews were conducted and participants were asked about risk factors for cervical cancer; women and generally better educated people had more knowledge (150). An association with social class ($p<0.001$) was found in Germany (151). In that study, age at first screening was associated with social class ($p<0.001$). Approximately 70% of the women considered themselves insufficiently informed about risk factors and only 3% knew that infection with HPV is a risk factor for cervical cancer. Another study assessed the proportion of women who had heard of human papillomavirus (HPV) in four Nordic countries (Denmark, Iceland, Norway, and Sweden) and examined correlates of this awareness (152). In this study, 60% of all participants had never heard of HPV. Correlates associated with having heard of HPV in the past included a history of genital warts (odds ratios, OR=2.57; 99% confidence intervals, CI: 2.38-2.76) and educational level (OR=2.06; 99% CI: 1.92-2.21). Another study, carried out in Sweden just before HPV vaccination was included in the Swedish national vaccination program,

concluded that overall knowledge of HPV among parents and young adults was modest, with a significant proportion of respondents not knowing or being uncertain about whether HPV can cause genital warts, cervical cancer and other cancers (153). Since most studies were carried out before the release of the HPV vaccine or introduction of the HPV vaccination program (2007-2010), general knowledge and awareness among populations may have increased. However, two European studies conducted in France and Germany concluded that knowledge about HPV and its relationship to cervical cancer was inadequate, and that there was a low prevalence of such awareness among young women (154, 155). In the study performed in France, only 14% mentioned HPV infection as the cause of cervical cancer, even though 76 % were aware of the HPV vaccine. Important correlates for acceptability of the HPV vaccine included knowledge about the vaccine and acceptance of other vaccines. In Germany, participants included female university students age 19-35 and a lower score on HPV knowledge (<median = 12, ranged 1-17) could be predicted among women in social sciences/humanities programs (OR = 3.68, 95% CI 1.99-6.79) and non-participants in cervical cancer screening (OR = 2.04, 95% CI 1.02-4.07).

2.4.2 Coverage and participation

Introducing HPV testing in primary screening will allow longer time intervals due to the test's high performance in detecting CIN2+. Health professionals are engaged in ongoing debate and speculation as to whether such testing will effect a change in behavior among women eligible for clinic-based screening. However, the literature contains no published evidence to this effect. Several countries practice either opportunistic screening or screening within the framework of an organized screening program, or a combination thereof to increase participation. In many countries, women must pay (net cash outlay) for spontaneous screening; since HPV testing is currently much more expensive than conventional cytology with Pap smear, screening inequalities could possibly arise between women in different socioeconomic classes. Hypothetically, women in higher socioeconomic classes would be more likely to choose HPV testing, while women in lower socioeconomic classes would choose a Pap smear. Two studies address this problem (156, 157). If Pap smear is not offered as an alternative, the high cost could deter women in lower socioeconomic classes from participation in screening. However, use of HPV self-sampling at a lower cost than clinic-based screening could increase participation among women in lower socioeconomic classes.

A small study of non-responders to the first invitation to clinic-based screening was conducted in Italy to investigate the feasibility of HPV self-sampling. Researchers concluded that there is acceptance for HPV self-sampling and that mailing a device for HPV DNA self-collection to non-responders as an alternative to conventional cervical cancer screening might increase compliance among the population, compared with repeated invitation to clinic-based cytology (158). The study reported a 5% increase in coverage, which is considered to be relevant in terms of public health (2% when only considering under-covered women whose last Pap smear was more than 5 years earlier). The 2005 Danish Health Technology Assessment of Cervical Cancer from Sundhedsstyrelsen et al. (159) found that a 1% absolute increase in the coverage rate achieves a similar or equal reduction of risk as

does reducing the screening interval from 3 to 2 years, an outcome with an estimated annual gain of 85 life-years in Denmark.

The future increase in population coverage or participation cannot be predicted based on existing literature. However, HPV self-sampling devices could potentially increase participation: higher performance in detection of CIN2+ and a reduced risk for developing cervical cancer following a negative HPV test will increase the safety of women who are not regular participants in the screening program. Consequently, this approach could reduce the incidence of cervical cancer and differences between socioeconomic groups. However, data are lacking on the possible increase in adverse outcomes, including unnecessary referrals for diagnostic follow-up and over-diagnosis, with subsequent overtreatment of lesions that may otherwise spontaneously regress. In the future, more research on adverse events is needed as HPV-based screening protocols replace the existing practice of conventional cytology-based cervical cancer screening.

2.4.3 Feasibility of HPV self-sampling

Previous studies have assessed the value of HPV-self sampling as a complement to conventional cytology. Specifically, the studies explored whether use of HPV self-sampling devices could increase screening coverage and participation among women who are nonparticipants or who do not participate regularly. Currently under debate is the use of HPV self-sampling as a follow-up method for secondary screening of women found to be HPV-positive and cytology-negative in primary screening. Successful HPV self-sampling requires a high level of acceptance among the population. Studies exploring acceptance of HPV self-sampling showed that apart from marital status, ethnicity and age, the most important correlate was high educational level (160-165). However, a Swedish study of women who had not attended the organized cervical cancer screening program for over 6 years found no significant difference in use of self-sampling based on age, country of birth, occupation or marital status. Attitudes toward HPV self-sampling differed among responders and non-responders. Women who performed HPV self-sampling were more positive toward self-sampling ($p < 0.01$) (166). Thus, acceptance was also found among non-responders (women who do not respond to screening invitations) (165, 167-169). Direct home mailing of the HPV self-sampling test was the preferred method to reach women (167, 170-172). One study with a large population sample examined HPV self-sampling as a method for primary screening and found that the participation rate was lower for the entire sample population compared with conventional cytology. However, when excluding women whose disease was detected through self-sampling and women who did not receive the HPV self-sampling kit by mail, the participation rate was almost 100% (173). Consequently, HPV self-sampling could possibly provide greater access to screening if the supporting administrative organization has accurate addresses for all women.

In conclusion, women of low socioeconomic status will be less likely to accept HPV self-sampling. However, HPV self-sampling may increase compliance across all socioeconomic groups. HPV self-sampling could also reduce overall costs for the organized screening program because of its low direct medical cost and because women can perform the test during their leisure time, avoiding loss of productivity and the other necessary direct non-

medical costs associated with time and travel incurred for clinic-based screening. Moreover, in countries where women pay for screening tests themselves there would be lower direct medical costs and fewer costs incurred by the women compared with clinic-based screening. Use of healthcare services in general, especially preventive health programs, is inversely related to the price the individual pays or the costs incurred. High prices and costs tend to deter use, while lower prices and costs encourage use of healthcare services (174). Consequently, HPV self-sampling could lead to higher participation or compliance among women who perceive costs associated with clinic-based screening to be high and who are therefore deterred from attending clinic-based screening.

2.4.4 Compliance with less frequent screening

Primary screening

Compared with the current 3-year screening interval for cytology-based testing, a 5-year interval is recommended with HPV testing following a negative test. To date, there are no studies to confirm compliance with the recommended 5-year screening interval in HPV testing. However, in Sweden a 5-year interval is used with conventional cytology for women aged 50-60, showing an overall high rate of compliance (84% within 5.5 years) (85). Shorter intervals are common in other countries that practice a combination of opportunistic screening and organized screening programs. A US study found that among all participants, 81% expected to have a Pap test within the year, while 91% of women whose most recent Pap test was within the past year expected to be screened again within 1 year (175). Another study found that 50% of women accept a 3-year Pap test interval, as do a 32% minority of physicians, while the majority of primary care physicians continue to recommend shorter intervals (176). This study showed an association between shorter screening intervals and higher socioeconomic levels. Should the problem of over-screening increase among women in higher socioeconomic levels, it is unlikely to be accompanied by an increase among women in lower socioeconomic levels. Among frequently screened women, a 5-year interval may seem too long and lead to increased use of spontaneous or opportunistic screening.

Secondary screening

The recommended follow-up period for repeat screening after an HPV-positive and cytology-negative test is from 6 months to 1 year. As implied by previous studies, socioeconomic status may influence compliance with the follow-up screening protocol. In one study of HPV-positive women with normal cytology who repeated the HPV test 1 year later, results show that immediate colposcopy is preferable to repeat HPV testing for monitoring of HPV infections (177). The preference for that alternative was associated with the desire for quick resolution and concerns about disease progression to cancer. Decreased compliance with follow-up may be related to the initial sampling technique depending on whether the initial sampling technique provides for reflex cytology (liquid based cytology) requiring no additional clinic visit, or whether further testing for cytology sampling requires women to

return to the clinic. In addition, problems may arise when an HPV-positive woman subsequently tests negative on cytology and is asked to return for further testing 1 year later in order to avoid unnecessary colposcopies and biopsies, as well as unnecessary treatments associated with further risk of adverse events. By using liquid-based cytology with co-sampling, HPV-positive women who are cytology-negative only need to return for follow up with a new HPV test 1 year later, thereby eliminating the need for an extra medical visit. One trial showed that compliance with repeat testing was slightly higher than trial baseline compared with subsequent rounds with colposcopy, showing a slight loss at follow-up (178). One study confirmed that personal counseling by phone increased compliance 1 year after an initial positive HPV test (179). Effective communication tools need to be developed to ensure compliance among HPV-positive women with negative cytology and should be made available to both women eligible for screening and physicians. Use of interventions to provide information help women make an informed decision and could potentially reduce over-screening (180, 181). Another strategy might be to discontinue insurance coverage for annual cytology tests when no indication is present. Additional approaches aimed at medical practices and at national health preventive program planning, include updating cervical cancer screening quality of care measures (i.e. screening history with test results) within national registries, which could then be used to evaluate performance and lead to more consistent recommendations concerning both spontaneous and opportunistic screening alone or in combination with organized screening.

2.4.5 HPV-positive results and how it affects woman

Several studies and reviews have addressed the anxiety experienced by women after a positive cytology test result (182, 183). Anxiety relates to disease progression, sexual function, body perception and future infertility. There are indications that that anxiety correlates with socioeconomic status. One study investigating the impact of abnormal Pap smear results on health-related quality of life (HRQL) showed that 35% of women from lower socioeconomic groups displayed clinically significant anxiety at 12 weeks, did not completely understand the information concerning their results and perceived themselves to be at higher risk of cancer (184). These findings imply that anxiety is associated with lack of knowledge about the disease and educational level. Such studies are also relevant for HPV-based screening where they may have even greater importance, since even higher proportions of women are HPV-positive (185). Also, concern over HPV as a sexually transmitted infection (STD) may affect sexual behavior and relationships (186). This may be especially relevant among less educated women who have difficulty understanding the relationship to cancer (187). Concern exists over how to effectively communicate a positive test result and general information about HPV (188, 189). In this regard, an Australian study showed that personal counseling is the preferred way to communicate tests results in order to reduce anxiety (190).

2.4.6 Combined screening and vaccination

There are concerns about preventive vaccination and screening in current and future generations. Some speculate that vaccinated women will defer screening as a result of altered attitudes toward screening (191-196). However, current knowledge of HPV suggests that the women at greatest risk are those who choose not to be vaccinated and those who do not participate in screening. One study that models screening outcomes was externally consistent with results from multiple and independent sources. Expected reductions in lifetime risk of cancer due to screening every year or every other year were 76% and 69%, respectively. The reduction from vaccination alone was 75%, although parameter uncertainty concerning the natural history of type-specific HPV infection is present (197). Screening participation and/or HPV vaccination is immensely important, but concern has been expressed that vaccinated women may alter the screening habits. Previous research has looked at whether prior experience of disease and screening participation by a woman's mother could affect women's future screening habits; the results are inconclusive (193-196, 198). One study of a representative sample in the British population (198) showed that screening attendance correlated with level of education (odds ratio [OR] = 1.66, confidence interval [95% CI]: 1.07-2.56) and marital status (OR = 2.04, 95% CI: 1.37-3.03). Acceptance of screening with HPV testing could be predicted by regular attendance for cervical cancer screening (OR = 1.58, 95% CI: 1.03-2.42) and by an ethnic white background (OR = 2.20, 95% CI: 1.18-4.13). The age of the daughter was the sole predictor of acceptance of HPV vaccination, while the mothers most likely to accept vaccination were those with daughters aged 13-16 (OR = 2.91, 95% CI: 1.27-6.65). A different study (193) showed that vaccinated women had a more positive attitude toward practicing safe sexual behavior, but less than 5% correctly identified cervical cancer screening guidelines. The findings from this study do not support previous research that the HPV vaccination program could have a negative impact on screening and sexual behavior. Another study examined the association between screening participation by mothers and vaccination of their daughters, and used a model simulation to estimate the effects of this on cancer incidence (195). The results showed that HPV vaccination status was significantly associated with screening participation by mothers (odds ratio: 1.54 [95% confidence interval: 1.51-1.57]). Only 13% of girls refuse to participate in either program, compared with 23% when screening alone is available and participation by the mother in screening was used as a proxy to determine the girls' future screening habits as adults. However, this model simulation only resulted in slightly lower estimates for the impact of vaccination on incidence of cancer, compared with estimates assuming no association. Empirical data concerning the above has yet to be published.

HPV vaccination is a preventive strategy for cervical cancer. However, cervical cancer screening must continue since the vaccines will not protect against the HPV types that are not included in the first generation vaccines. HPV testing as primary screening is still relevant for vaccinated women (199). Further research on vaccinated women and screening algorithms will help define future preventive policies for cervical cancer and possibly for other HPV-related cancers as well.

3 AIMS OF THE THESIS

3.1 GENERAL AIMS

The aims of the thesis were to study the efficiency in the allocation of resources to cervical cancer screening of importance for setting priorities: the cost of the most prevalent HPV related diseases namely cervical dysplasia, cervical cancer and genital warts, modeling the cost-effectiveness of cervical cancer screening and exploring knowledge of HPV, compliance with screening and its correlates.

3.2 SPECIFIC AIMS

The specific aims of the thesis were as follows:

3.2.1 Paper I

To evaluate the cost-effectiveness of human papillomavirus testing (HPV triage) for follow-up and management of women with index smear diagnosis of ASCUS and LSIL within the framework of the Swedish organized screening program.

3.2.2 Paper II

From a societal perspective, to evaluate the cost-effectiveness of HR-HPV testing using self-collected vaginal samples within the framework of the Swedish organized screening program.

3.2.3 Paper III

This study aims to identify possible barriers to and facilitators of cervical cancer screening by (a) estimating time and travel costs and other direct non-medical costs incurred by women attending the clinic-based cervical cancer screening program, (b) investigating screening compliance and reasons for noncompliance, (c) determining women's knowledge of human papillomavirus (HPV), its relationship to cervical cancer, and HPV and cervical cancer prevention, and (d) investigating correlates of HPV knowledge and screening compliance.

3.2.4 Paper IV

The present study is aimed at estimating costs for prevention, management and treatment associated with cervical dysplasia, cervical cancer and genital warts from a societal perspective in Sweden in 2009, 1 year before implementation of quadrivalent HPV vaccination program.

4 MATERIALS AND METHODS

4.1 MODELING COST-EFFECTIVENESS OF HPV TRIAGE FOR FOLLOW UP OF WOMEN WITH MINOR CYTOLOGICAL ABNORMALITIES (PAPER I)

4.1.1 Modeling approach

We created a decision tree-based model to evaluate the cost-effectiveness of three follow-up strategies from a health care perspective:

Follow-up strategies for women with index smear diagnosis of ASCUS and LSIL detected in the organized screening program at local outpatient clinics:

- A) **Cytology** includes a visit to a gynecologist for a repeat Pap smear. When cytology result shows cytological abnormality, with ASCUS as the cut-off, the women are referred for a third follow-up visit to a gynecologist for colposcopy with biopsy. If the follow-up with Pap smear is within normal limits, the woman is referred back to the organised screening program for a new Pap smear 3 or 5 years later (depending on age).
- B) **HPV triage** includes a follow-up visit to a midwife for HPV testing with HC2 (Hybrid Capture 2®, Digene Corporation, Gaithersburg, Maryland, USA). All HR-HPV-positive women are referred for a third follow-up visit to a gynecologist for colposcopy with biopsy. All HR-HPV-negative women with index smear diagnosis of ASCUS or LSIL are referred back to the organised screening program for a new Pap smear 3 or 5 years later (depending on age).
- C) **Immediate colposcopy with biopsy** includes a visit to a gynecologist for examination including colposcopy and directed biopsies. If there is no colposcopically visible lesion a biopsy is taken. This follow up strategy were assumed to have the highest sensitivity and specificity 100% (i.e., the gold standard), and constitutes the reference examination for diagnosing CIN.

The time frame for the study was one year from index smear diagnosis of ASCUS and LSIL in the organized screening program.

4.1.2 Population and setting

Data on test accuracy which populated the model were data from one clinical trial performed within the Swedish organized screening program (200). The women had undergone screening with Pap smear taken by a midwife at a local outpatient clinic according to current policy and practice. The study group within the clinical trial consisted of 177 women aged 23 to 60 years with a diagnosis of ASCUS or LSIL on the index smear. They were all referred for gynecological examination because of the aforementioned screening results. The mean age of the women was 34 years. The group consisted of 177 women and was subdivided according to age and ASUS or LISL on index smear; women of

all ages (23–60 years), women up to age 30 and women aged 30 years and older with diagnose ASCUS/LSIL considered as one group and ASCUS and LSIL as two separate groups.

4.1.3 Health economic data

The effect data was based on prevalence of HR HPV, prevalence of CIN2+ and the different screening test performance (i.e. sensitivity and specificity). Screening tests included in the follow-up strategies were repeat conventional cytology with Pap smear, HPV testing with HC2 (Hybrid Capture 2) and colposcopy with biopsy (i.e. the gold standard).

Table I.1 Prevalence of HR HPV, CIN2+ and performance of follow-up strategies

Parameter a)	All women	Women <30 years	Women ≥30 years
ASCUS/LSIL			
Prevalence, CIN2+	0.21	0.23	0.20
Prevalence, HR-HPV	0.66	0.81	0.54
Sensitivity for CIN2+			
Cytology	0.61	0.50	0.70
HPV triage	0.82	0.89	0.75
Specificity for CIN2+			
Cytology	0.56	0.52	0.59
HPV triage	0.39	0.22	0.52
ASCUS			
Prevalence, CIN2+	0.19	0.17	0.21
Prevalence, HR-HPV	0.44	0.67	0.32
Sensitivity for CIN2+			
Cytology	0.60	0.67	0.57
HPV triage	0.60	0.67	0.57
Specificity for CIN2+			
Cytology	0.69	0.60	0.74
HPV triage	0.60	0.33	0.74
LSIL			
Prevalence, CIN2+	0.22	0.25	0.20
Prevalence, HR-HPV	0.74	0.85	0.65
Sensitivity for CIN2+			
Cytology	0.61	0.47	0.77
HPV triage	0.89	0.93	0.85
Specificity for CIN2+			
Cytology	0.51	0.49	0.52
HPV triage	0.30	0.18	0.40

“a)Colposcopy with biopsy is referred to as gold standard”

The cost data included average unit costs for the different quantities obtained from local and nationwide sources in Sweden. All costs were based on “Patient-level Clinical Costing” (known as cost per patient (KPP) in Sweden). All costs in the study were expressed in 2008 Swedish Kronor (SEK). Costs were not discounted due to the short time frame of only one year.

4.1.4 Sensitivity analysis

A one way sensitivity analysis was conducted varying the model parameters to examine when HPV triage becomes a cost-effective alternative. Due to the uncertainty in the data on sensitivity and specificity from the clinical trial data, data on the accuracy of HPV triage for detection of CIN2+ were complemented with accuracy presented in published meta-analyses (201-204).

4.2 MODELING COST-EFFECTIVENESS OF HPV SELF-SAMPLING IN PRIMARY SCREENING (PAPER II)

4.2.1 Modeling approach

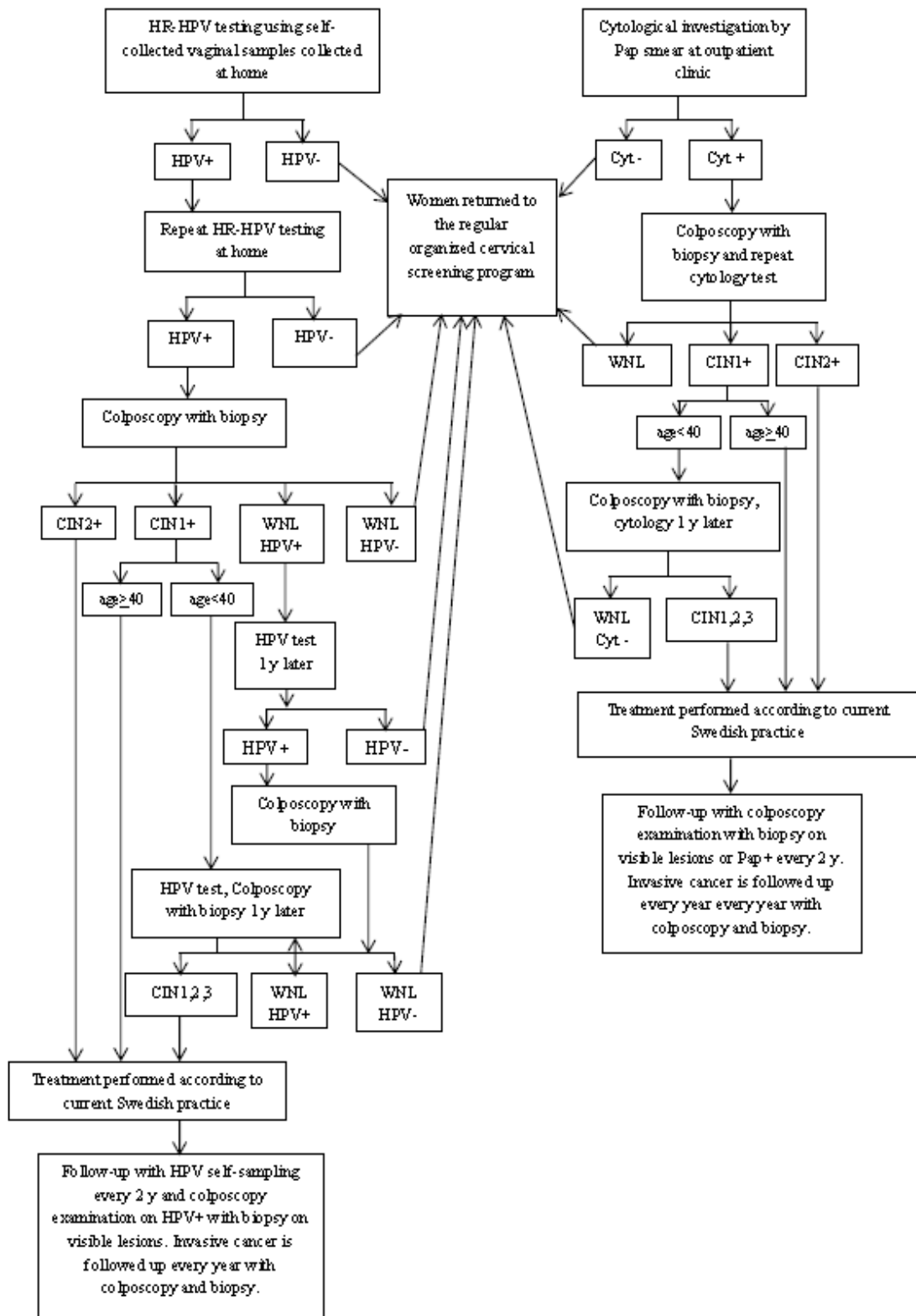
A Markov simulation model was developed to simulate the natural history of HPV, cervical dysplasia and cervical cancer. The model included following health states: healthy (i.e. no ongoing HPV infection), ongoing HPV infection, CIN1, CIN2+ and cervical cancer subdivided into the FIGO stages I, II, III and IV. In the model, women started out as healthy at age 15. Health states then altered according to a set of probabilities that occurred within predetermined yearly cycles until the women reached age of 85 years or died from either cervical cancer or other causes. The women was every yearly cycle at risk of attaining an infection with HPV via sexual transmissions, which with time could progress to CIN1 or CIN2+, continue being in a persisting state or clear. CIN1 or CIN2+ lesions could either regress to a healthy status, continue being in same state or progress their disease to invasive cervical cancer. The women that progressed from cervical dysplasia to invasive cervical cancer could progress from a FIGO stage I to a more advanced FIGO stage (II–IV). Women with FIGO stage I–IV could be diagnosed through screening or by presenting with symptoms. Simplifications of the model were necessary; women with an ongoing HPV infection, CIN1 and CIN2+ could only have their infection or lesions detected during screening; cervical cancer survivors could only die from causes other than cervical cancer.

Screening strategies with alternative frequencies with 2, 3, 3/5 and 5 years' time interval between the screening opportunities:

- A) A **combination strategy** including conventional cytology with Pap smear from the age of 23 until age 34 and HPV self-sampling performed by the women themselves in the privacy of their home from age of 35 until 60 years. The women were assumed to be using a “Viba-brush (Rovers Medical Devices, B.V., Oss, the Netherlands)” for the procedure of collecting cells which they afterwards applied on to an indicating “FTA™ Elute Micro Card (GE Healthcare, Chalfont St Giles, UK)”, and thereafter mailed in for HPV analysis with “RT-PCR, detecting HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59” as previously described in detail (114-116).
- B) **Conventional cytology** with Pap smear between age 23 and 60 years.
- C) **Status quo** means screening with conventional cytology with Pap smear between age 23 and 60 years at 3-year/5-year intervals according to current screening policy on age and time intervals of today.
- D) **No screening** offered to the women population which was used as reference strategy for the model validation.

Follow up and screening protocols were set according to Swedish for screening and practice (see Figure II:1.)

Figure II:1. Screening, management and follow up applied in the model structure.



4.2.2 Population and setting

The model was populated with an assumed Swedish female cohort of all women aged 15 to 85 years. Women were eligible for screening between age 23 and 60. All different screening strategies and follow-up were assumed to be under control of the organized cervical cancer screening program.

4.2.3 Validation of the model

For validation of the model we used “no screening” as our reference strategy. We computed the model by changing the age-specific incidence rate of HPV infection within a relevant range to extrapolate the average annual cervical cancer incidence rates from the time before screening was initiated in Sweden. Conventional cytology was then added to reflect current screening policy and practice, population coverage and screening test accuracy. The internal validity of the model was then tested by comparing the model projected outcomes on cervical cancer incidence rate with the conventional cytology screening strategy based on empirical data following the implementation of organized cervical cancer screening in Sweden (1961–2009) with the “no screening” alternative. According to this comparison of strategies, outcome results of cervical cancer cases closely resembled the empirical data, with a similar peak age group.

4.2.4 Health economic data

Data for the model was; age-specific incidence of HPV infection, transition probabilities between the predetermined health states; survival rates for cervical cancer after treatment and mortality rates derived from previously published literature and chosen by clinical experts for inclusion (13, 14, 26, 205-212) (see Table II:1). The relative mortality risk from other causes was obtained from Swedish official statistics (available in English at <http://www.scb.se>) while the age-specific incidence and mortality rates for cervical cancer in Sweden were collected from IARC (213-216). Data on test accuracy in the base case analyses were taken from previously published data (114-116).

Cost data were incorporated into the model using a societal perspective. We therefore included both direct medical costs and indirect costs. The productivity loss due to cervical cancer screening, diagnosis, management and treatment was based on an average monthly gross wage rate. All costs were expressed in 2011 Euro (€). Direct costs were mainly based on “Patient-Level Clinical Costing”, (KPP in Swedish), as previously described in Paper I and supplemented with the direct medical costs for the HPV sampling kit and virus typing at Uppsala University Hospital. Costs for diagnosis of cervical cancer, the procedure for staging and treatment of invasive cervical cancer by FIGO stage were obtained from records at Radiumhemmet, Karolinska University Hospital. All future costs were discounted to present value at 3% annually. According to published recommendations, we also included the cost of added life-years in the model (56, 217).

Table II.1. Model parameters

Model parameter	Base-case analysis
Natural history	
Well to HPV*	0.01-0.22
HPV to Well by age (y); 15-29/30-65/ ≥ 66	0.9/1y/0.4/1y/0.2/1y
HPV to CIN1	0.2/3 y
HPV to CIN2+	0.05
CIN1 to Well	0.9
CIN1 to CIN2+ by age (y); 15-34/ ≥ 35	0.1/6 y/0.35/6 y
CIN2+ to CIN1	0.35/6 y
CIN2+ to Well	0.5
CIN2+ to FIGO I	0.4/10 y
FIGO I to FIGO II/annual probability of symptoms/5-y SR	0.9/4 y/0.15/0.84
FIGO II to FIGO III/annual probability of symptoms/5-y SR	0.9/3 y/0.225/0.66
FIGO III to FIGO IV/annual probability of symptoms/5-y SR	0.9/2 y/0.6/0.38
FIGO IV annual probability of symptoms/5-y SR	0.9/0.11
HR HPV strategy; Sensitivity for CIN1+/Specificity for CIN1+	1.0/0.98
Conventional cytology; Sensitivity for CIN1+ /Specificity for CIN1+	0.75/0.72
Coverage	0.80
Follow up of HPV-positive or any abnormality	1.0
Follow up of treatment of CIN or invasive cancer	1.0

*“*In the model, we do not distinguish between different HPV types. Incidence, progression and regression represent an average value for all HPV types.”*

4.2.5 Sensitivity analysis

Due to the uncertainty in the model parameters, costs and effects were altered in the sensitivity analysis to investigate the impact on cost-effectiveness results. In additional analysis, quality of life weights were included for each FIGO state in the model for the duration of time spent in that state.

4.3 INVESTIGATING BARRIERS AND FACILITATORS TO COMPLIANCE IN CERVICAL CANCER SCREENING (PAPER III)

4.3.1 Study design, population and data collection

This descriptive population-based study included 1 510 women aged 23-60 attending the organized screening program at five different local outpatient clinics in Stockholm, Sweden. Self-administered questionnaires were handed out and completed by women in the waiting room at the outpatient clinics. Data were collected from March 2013 to April 2014. The study was approved by the Ethical Review Board at Karolinska Institutet, Stockholm, Sweden.

Questionnaire

To investigate barriers to and facilitators of compliance with clinic-based cervical cancer screening we constructed a questionnaire based on the recommendations of a working group on patient-reported costs (218), and influenced by previous described questionnaires used in studies on knowledge and attitudes toward HPV(152, 153, 219). The questionnaire was refined through a validation process.

The first part of the questionnaire explored sociodemographic characteristics (age, marital and employment status, income and educational level). *The second part* of the questionnaire investigated time and travel costs and other direct non-medical costs, including mode(s) of transport to and from the clinic, time spent traveling, estimated distances, estimated net cash outlay for mode(s) of transport, ticket fares, parking fees, child care expenses, and activities before attending screening. This part also contained questions about estimated time taken off from work to attend screening; if the woman was accompanied, the companion's relationship to the woman; income level and estimated time off work were also considered.

We also measured the average waiting and procedure time at two outpatient clinics on 4 separate occasions. Time was measured with a stop watch from time of arrival until departure the clinic. *The third part* of the questionnaire explored knowledge about the purpose of screening, if the women were satisfied with the invitation letter, compliance (screening attendance within one year from initial invitation) and reasons for noncompliance, knowledge about HPV, cervical cancer screening and the relationship to cervical cancer, as well as prevention methods such as screening and vaccination.

4.3.2 Statistical analysis

Prior to study start, we conducted a power calculation for sample size and determined that a study sample of 1500 responders would ensure a power of 0.976 to detect a difference in the proportion of women from different age groups concerning HPV knowledge. Data were entered into the Statistical Package for Social Science (SPSS software version 21.). Descriptive statistics including frequency distribution of variables and mean scores were obtained. To test internal data reliability, Cronbach's alpha coefficient was measured and an alpha ≥ 0.70 was considered to be satisfactory. Mean differences for travel mode costs, and

distances were analyzed by one-way analysis of variance at the 5% significance level, with a Bonferroni correction. The Z-test was used to identify if sociodemographic characteristics differed significantly on some single (categorical) characteristic in the respondents compared to the whole female population. Also, we investigated if knowledge of HPV between age groups differed significantly by using the Z test.

A binomial logistic regression model was used to investigate correlates of HPV knowledge and compliance with screening. For questions, we assigned a value of 1 to a Yes response (i.e. correct) and a value of 0 to No and Don't know responses (i.e. incorrect responses). Correlates of knowledge were determined using a dichotomous dependent variable based on the median (i.e., ≥ 5 or < 5) HPV knowledge score. We performed a manual backwards stepwise procedure to determine the remaining variables in the model. Non-significant variables were excluded from the model. Variables were retained if their removal altered the width of the confidence intervals (CIs) of the other remaining variables by more than 10%. Qualitative data obtained from individual answers were used to support the quantitative data.

4.4 ESTIMATE COST OF PREVENTING AND MANAGING HPV-RELATED DISEASES BEFORE THE INTRODUCTION OF QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINATION (PAPER IV)

4.4.1 Study design, population and data

A cost-of-illness study approach was applied (63) to estimate the total cost of prevention, management and treatment of cervical cancer and genital warts in Sweden from a societal perspective. We investigated costs incurred over a given one-year (2009) time period, regardless of date of onset. Data were collected from the target study population and cost estimates were extrapolated to be representative of the entire population using national prevalence estimates. Cost categories included: costs for medical procedures and management, inpatient and outpatient care, tests and drugs, as well as costs resulting from productivity loss (sick leave, absence from work). Swedish data on costs and prevalence of cervical cancer and genital warts were collected from the following sources: KPP (Swedish cost per patient database), Statistics Sweden (SCB), Eurostat database and the Dental and Pharmaceutical Benefits Agency (available in English at <http://www.tlv.se>), as well as published epidemiological and cost data. Where no data were available, best possible estimates or extrapolated data were used in the study. Register data on genital warts are lacking, since they are not included in Sweden's mandatory surveillance of infectious diseases. Therefore, epidemiological data from a recent study based on prescription drug registers and patient registers (220) and published data from the United Kingdom were used to estimate rates of genital warts (221).

4.4.2 Investigating procedure and management of genital warts

Regarding genital warts, to estimate treatment patterns, average number of visits, and time spent for each type of procedure, we developed a standardized questionnaire and sent it to 10 physicians with extensive clinical experience in managing and treating patients with genital warts. The clinical expert panel included physicians from various specialties (general medicine, dermatology/venereology, gynecology/obstetrics) from both the outpatient and inpatient settings. Following completion of questionnaires, physicians in the expert panel were interviewed to review responses as necessary. The responses were pooled, and means, medians and ranges were calculated. Treatment patterns were constructed from the mean values and then used to determine costs. Estimates of travel time to and from care facilities and waiting time were taken from our previous study (travel to the clinic for screening: 44 min; waiting time: 10 min) (paper III).

4.4.3 Validity

Cost analysis results were tested for internal and external validity as follows: sensitivity analysis was used to test assumptions made (internal validity) and estimated costs were compared with previous findings in the published literature (external validity).

5 RESULTS AND DISCUSSION

5.1 COST-EFFECTIVENESS OF HPV TRIAGE FOR FOLLOW UP OF WOMEN WITH MINOR CYTOLOGICAL ABNORMALITIES (PAPER I)

5.1.1 Cost effectiveness results

Given that the Swedish society accepts and is willing to pay the additional cost, colposcopy with biopsy as follow-up and management of women with index smear diagnosis of ASCUS or LSIL was considered a cost-effective option, in comparison to HPV triage and repeat cytology. For women 30 years and older with index smear diagnosis of ASCUS, HPV triage was the least costly alternative in comparison to both strategies although with equal health effect as repeat cytology. In the same index cytology and age group, colposcopy with biopsy detected 88 more CIN2+ cases per one thousand women with a cost-effectiveness ratio of SEK 2 056 per additional health effect compared with HPV triage.

For women with index smear diagnosis of ASCUS and LSIL considered as one group, from 30 years and older, HPV triage detected 11 more CIN2+ cases per one thousand women, and was less costly in comparison to repeat cytology. For women with index smear diagnose of LSIL from 30 years and older, HPV triage detected 15 more CIN2+ cases per one thousand women and was only slightly less costly in comparison with repeat cytology. For women below the age of 30 years, regardless of index cytology, HPV triage was the most costly follow-up strategy, although with equal or higher health effect than repeat cytology. For women with index smear diagnosis of ASCUS and LSIL considered as one group, in all ages, HPV triage was more effective than repeat cytology detecting 45 more CIN2+ cases per one thousand women, although more costly.

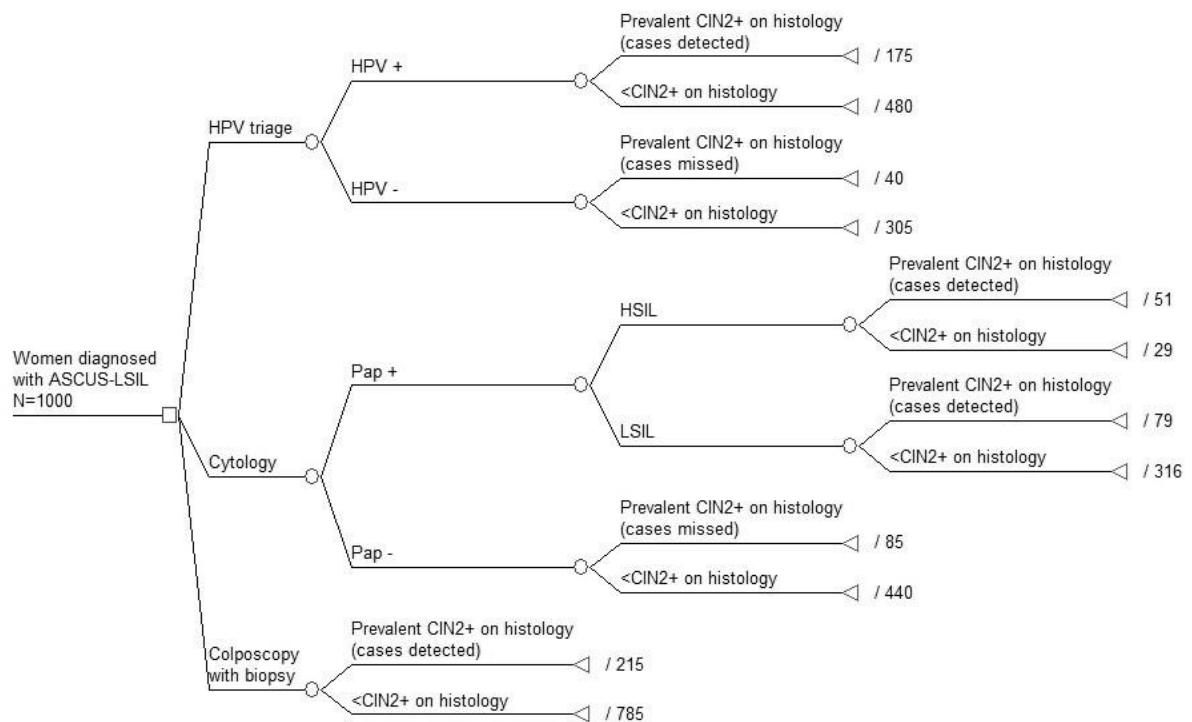
When comparing HPV triage with immediate colposcopy with biopsy, we found that for women with index smear diagnosis of ASCUS and LSIL considered as one group in all ages, HPV triage was less effective detecting 40 less CIN2+ cases per one thousand women and more costly. The largest difference in costs between these two strategies was seen for women with index smear diagnose of LSIL below 30 years of age, where HPV triage was SEK 1 098 more costly and detected 17 less cases of CIN2+ per one thousand women. The smallest difference in costs was seen for women with index smear diagnose of ASCUS for women in all ages, where HPV triage was only SEK 106 more costly than colposcopy with biopsy, although detecting 77 less CIN2+ cases per one thousand women.

Table I.2 Cost-effectiveness results for the follow-up strategies in different subgroups according to index cytology and age.

Follow-up strategy	Cost ^a (SEK)	Incremental Cost ^a (SEK)	CIN2+ cases detected ^a	Incremental Effectiveness ^a	Incremental Cost Effectiveness Ratio ^{a, b, c}
ASCUS/LSIL					
All women					
Colposcopy with biopsy	2 432		215		
Cytology	2 928	496	130	- 85	Dominated
HPV triage	3 057	625	175	- 40	Dominated
<30 years					
Colposcopy with biopsy	2 432		231		
Cytology	2 959	527	115	- 115	Dominated
HPV triage	3 427	995	205	- 26	Dominated
≥30 years					
Colposcopy with biopsy	2 432		202		
HPV triage	2 765	333	152	- 51	Dominated
Cytology	2 904	472	141	- 61	Dominated
ASCUS					
All women					
Colposcopy with biopsy	2 432		192		
HPV triage	2 538	106	115	- 77	Dominated
Cytology	2 662	230	115	- 77	Dominated
<30 years					
Colposcopy with biopsy	2 432		167		
Cytology	2 856	424	112	- 55	Dominated
HPV triage	3 085	653	111	- 56	Dominated
≥30 years					
HPV triage	2 251		118		
Colposcopy with biopsy	2 432	181	206	88	SEK 2 056 /CIN2+ case ^a
Cytology	2 562	130	118	- 88	Dominated
LSIL					
All women					
Colposcopy with biopsy	2 432		224		
Cytology	3 039	607	136	- 88	Dominated
HPV triage	3 272	840	200	- 24	Dominated
<30 years					
Colposcopy with biopsy	2 432		250		
Cytology	2 990	568	117	- 133	Dominated
HPV triage	3530	1 098	233	- 17	Dominated
≥30 years					
Colposcopy with biopsy	2 432		200		
HPV triage	3 034	602	169	- 31	Dominated
Cytology	3 084	652	154	-46	Dominated

“The follow-up strategies are ordered by increasing costs. Incremental cost, CIN2+ cases detected (effectiveness) and incremental cost-effectiveness ratio (ICER) are calculated relative to the next less costly follow-up strategy. ICER is calculated according to the following equation: $ICER = (Cost\ of\ screening\ strategy\ A - Cost\ of\ screening\ strategy\ B) / (Effect\ of\ screening\ strategy\ A - Effect\ of\ screening\ strategy\ B)$. Dominated strategies are those with higher costs and lower clinical efficiency than other strategies.”

Figure I.1. Decision tree.



“A simplified decision tree of follow up strategies presenting one thousand women in all ages with index smear diagnosis ASCUS/-LSIL built on data from one single trial by Andersson et al 2005. The outcome shown in the figure is the number of detected or missed CIN2+ cases for each of follow up strategy.”

5.1.2 Sensitivity analysis

According to the sensitivity analysis, the results were most sensitive to varying costs for the HPV test. For women with index smear diagnosis of ASCUS and LSIL considered as one group and for women in all ages, HPV triage was a less costly and next most effective follow-up strategy below SEK 231 for the HPV test cost and below SEK 522 for women 30 years and older, while repeat cytology was a dominated alternative in all variations. For women with index smear diagnose of ASCUS considered as one group and all ages, HPV triage was the less costly below SEK 749, and below SEK 1 035 for women 30 years and older.

5.1.3 Discussion

At the time of this study, the Swedish guidelines recommended immediate colposcopy with biopsy as follow-up of ASCUS and LSIL/CIN1 for all women below the age of 35 years and HPV triage for women 35 years and older. Repeat cytology with Pap smear was not a recommended follow-up strategy due to a low sensitivity to detect CIN2+. However, repeat

cytology is still practiced as a follow-up method by either midwife at local outpatient clinics or by gynecologists depending on county council residence.

Previous research has shown that significant costs evolve from unnecessary follow-up of women at low or no risk of developing cancer since a large proportion of the women are healthy or LSIL with spontaneous resolution (222). Therefore HPV triage could be considered a less aggressive approach for follow-up. Only women with persistent infections of HPV should be further examined with less aggressive protocols which are adapted to the actual risk of developing CIN3 or cancer (223). However, there are concerns of compliance to screening protocols regarding over and under screening, the association to SES and especially for cytology negative and HPV positive women. Anxiety induced of a HPV positive and cytology negative result when there is no immediate need for follow-up could be influenced by SES and knowledge of HPV. In a previous study, results showed that women preferred immediate colposcopy instead of continued follow-up with HPV testing (177). SES and knowledge about HPV could possibly influence compliance to putative screening algorithm.

This study is based on data from a clinical trial and one important limitation with use of clinical trial data is their short duration. It is important to consider long-term consequences when assessing the cost-effectiveness of a screening strategy. This patient population is at risk of over-diagnosis and overtreatment; moreover, adverse events may occur. Such concerns should be monitored for a longer time period. However, no modeling studies concerning long-term risk of adverse events have yet been published.

It is important to assess the relevance of the alternatives used in the model. When Paper I was written, women with index smear diagnosis of ASCUS and LSIL were commonly followed up by repeat Pap smear performed by a midwife/gynecologist or in some county councils such as Stockholm, by immediate colposcopy with biopsy. Based on previous research in population-based clinical trials (224) HR-HPV testing was considered to be a future alternative for follow-up (secondary screening). Comparison of these alternative follow-up methods was therefore highly relevant for economic evaluations being valuable material for making informed decisions about choice of follow-up procedures within the organized screening program.

Recently, triage of ASCUS using HR-HPV testing showed high sensitivity for detection of CIN2+ and a high negative predictive value after 3 years of follow-up (225). Internal validity of the clinical trial was high since the study sample was based on CIN2-3, the clinical cut-off for treatment of precancerous lesions, and generated a large outcome in a relatively small study population. However, in this clinical trial, performance of Hybrid Capture 2 (HC2) was low compared with other studies (90, 201). The uncertainty of the parameters regarding test performance was therefore evaluated using data on HC2 from the previously mentioned Meta-analyses. However, the overall cost-effectiveness results did not change. Nevertheless, external validity and generalizability to other settings is high since the alternative strategies are currently practiced in countries with organized screening programs.

Choice of perspective determines which costs and health benefits to include in the analysis. This study was performed from a Swedish health care perspective and only included direct medical costs. However, a broader perspective (societal perspective) that includes all costs is

recommended for economic evaluations to assist decision-making on the societal efficiency in the allocation of health care resources. Also, cervical cancer have a broad impact on a wide range of personal and individual dimensions such as women's health, the quality of life, work ability, social and sexual relations, physical function and income level which should all be considered in health economical evaluations. However, even though this study uses a narrower perspective (health care perspective), for countries with similar organized screening as in Sweden, it provides important information for decision-makers about issues regarding costs and effects when they consider whether to include HR-HPV DNA testing in current follow-up strategies. All direct medical costs for the follow-up strategies under comparison were based on Patient-level Clinical Costing (known as cost per patient (KPP) in Sweden), a methodology used to calculate the cost of each hospital stay or office visit for the individual patient. The method describes healthcare consumption from the perspective of diagnosis and is useful for decision making at all levels in the Swedish healthcare sector. This includes variable costs (costs related to time required for healthcare professionals and equipment), and fixed or overhead costs (e.g. costs for power, heat, rent and capital). However, these costs only reflect the estimated costs for the hospital environment, while excluding outpatient costs. The costs may therefore be overestimated compared with follow-up care provided in the outpatient setting. Thus, throughout Sweden follow-up and treatment is often provided in the hospital setting, rather than in outpatient clinics.

Regarding effect data, use of sensitivity and specificity to detect CIN2+ lesions, is relevant and mandates follow-up in order to minimize the risk of developing invasive cervical cancer. Requirements for HPV triage to be an appropriate follow-up strategy of women with ASCUS and LSIL are high sensitivity and negative predictive value to detect CIN2+. Today, Swedish guidelines recommend use of HPV triage on women with minor cytological abnormalities (ASCUS and LSIL/CIN1) from age 35 and older. In our study all women in all ages were referred for colposcopy and biopsy. Results confirmed previous study results that HPV triage is not cost-effective under the age of 35. Results showed that HPV triage is dominated by immediate colposcopy and biopsy in all age groups and index cytology except among women over 30 years with ASCUS. For women with LSIL, regardless of age, HPV triage was not considered a cost-effective alternative. The clinical trial found that HC2 testing detected 74% HPV positive women and 26% HPV negative women with index smear diagnose of LSIL which is low since only 5 to 10% are estimated to be negative for HPV infection according to previous research (201). The possible explanation for a larger percentage HPV negative could be explained by unadequate sampling, an infection with non-oncogenic HPV not targeted by HC2, false positive results or false negative HPV tests and spontaneous resolution. Today, both European and American guidelines do not recommend HPV triage for women with LSIL but of women with ASCUS. However, when deciding up on revised guidelines for referrals of women with ASCUS or LSIL to colposcopy and biopsy one should consider the recent Cochrane review presenting significantly higher sensitivity for HC2 to detect CIN2+ and CIN3+(108).

To deal with the uncertainty in the costs and consequences addressed by this study we performed a one-way sensitivity analysis to examine when HPV triage becomes a cost-effective alternative. When varying parameters for the follow-up strategies, the model result was most sensitive to changes in cost for the HPV test. A one-way sensitivity analysis could

be an inadequate approach due to overall uncertainty in the cost-effectiveness ratio depending on the combined variability of several variables. However, this analysis only used a few key variables in the base case and therefore a one-way analysis was assumed to be adequate to address uncertainty in this study.

In this evaluation, all HR-HPV-positive women were assumed to be referred for colposcopy with biopsy. By only targeting women with the most oncogenic HR-HPV types, HPV-genotyping could further reduce the number of women referred for colposcopy with biopsy. Moreover, with a higher performance of HR-HPV testing and reduced referral rates for colposcopy with biopsy, HPV ‘reflex genotyping’ could also become a cost-effective alternative follow-up strategy in the Swedish organized screening program. However, this has yet to be further evaluated.

HPV triage was according to this study result a preferred follow-up strategy compared with repeat cytology for follow-up of ASCUS and LSIL among women 30 years and older. With use of liquid-based cytology instead of repeat Pap smear within the organized screening program, HPV testing can be performed on existing sample (HPV reflex testing) which avoids the costs for an additional physician visit and could therefore be a cost-effective alternative to HPV triage. However, results from one study concluded that HPV triage with “two follow-up visits” (as in our study), was cost-effective compared with repeat cytology and immediate treatment (226). According to results from another cost-effectiveness study showed contrary results, that HPV reflex testing was a more effective and less costly strategy than HPV triage (with two follow up visits), repeat cytology and immediate colposcopy initially diagnosed with ASCUS (227). Similar results were also found in other cost-effectiveness analyses that HPV reflex testing in cases of ASCUS, was cost-effective in women of all ages (228, 229).

5.2 COST-EFFECTIVENESS OF HPV SELF-SAMPLING WITHIN THE FRAMEWORK OF THE ORGANIZED SCREENING PROGRAM (PAPER II)

5.2.1 Cost-effectiveness result

The overall projected model outcome showed that the cost effectiveness ratio for the combination strategy, depending on time interval between the screening opportunities ranged between; “€43 000 to €180 000 per LYG without the cost of added life-years, and between €74 000 and €206 000 with the costs of added life-years”. The cost-effectiveness ratio for the combination strategy at a 5-year time interval, both with and without the cost of added life-years, were beneath the chosen threshold value , indicating that this is a potentially cost-effective screening approach compared with conventional cytology, status quo strategies and the alternative of no screening .

Figure II:1. Cost-effectiveness result of different screening strategies at different intervals.

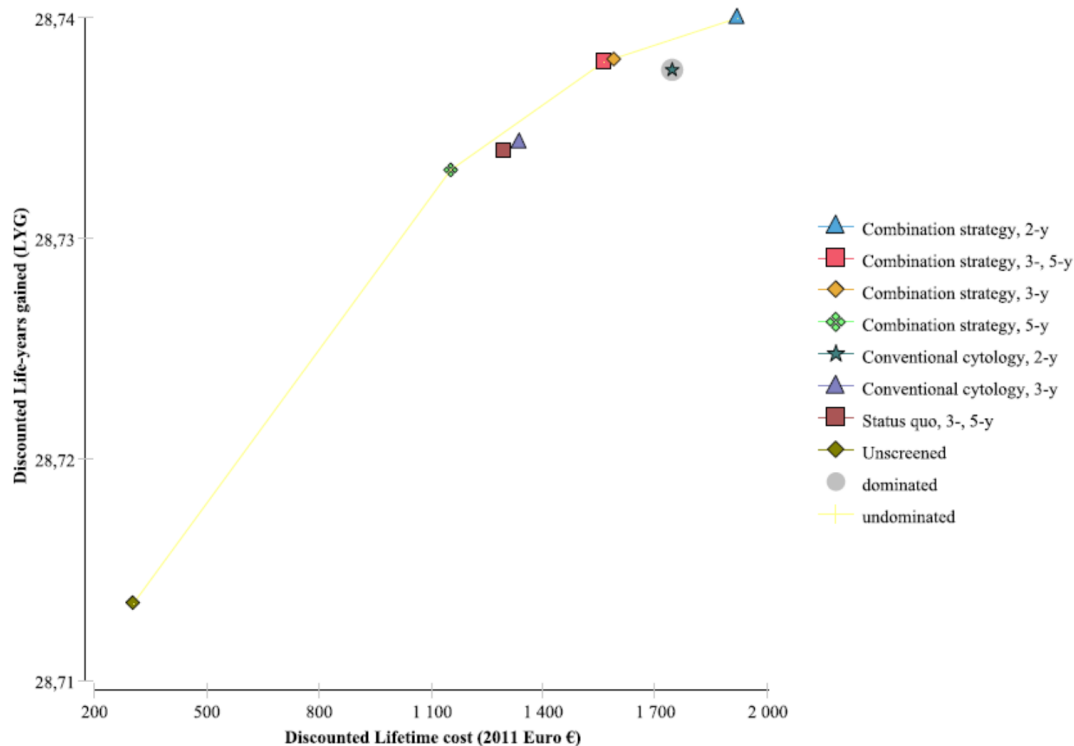


Figure legend: “Cost-effectiveness of different screening strategies at different screening intervals: base-case analysis without the cost of added life-years.”

5.2.2 Intermediate outcomes

The model projected a reduction of the cervical cancer risk of 56% with the combination strategy at a 5-year interval, and 75% at a 3/5-year interval. For the status quo strategy with a 3/5-year interval the reduction was 48% which is similar to results presented in other studies that performed model projections of HPV testing vs. cytology testing (228, 230). The model projections of intermediate outcomes of age-specific HPV prevalence among the group of

women with normal cytology test result peaked at 27% at the years near the age of 20 years. From an age-specific standpoint, peak prevalence of cervical dysplasia was almost 4% at the age of 34, with a second peak at age 43 of around 3%. Our model projected an average prevalence of cervical dysplasia similar to the prevalence previously reported in a Swedish population (224), and in a clinical study population (114). The rate of cervical dysplasia detected by screening according to the status quo strategy was similar to rates shown in a previous report from Sweden (231). Referral rates for colposcopy and biopsy without findings of cervical dysplasia or cervical cancer were 35% higher for the combination strategy using a 3/5-year interval compared with a 5-year interval, which is similar to results presented in another study (232).

Table II:2. Average life time cost, life time expectancy (discounted at 3% and undiscounted, reduction on cervical cancer risk and ICER (€)/LYG.

Screening strategy	Average lifetime cost (€)	LYG, d 3% ^a	LYG, 0% ^a	CC risk, %	ICER, €/LYG ^{b,d,e}	ICER with cost of added life-years, €/LYG ^{c,d,e}
No screening	303	28.7135	65.6275	—	—	—
Combination strategy, 5-y	1 151	28.7331	65.7108	56.0	43 000	74 000
Status quo strategy, 3/5-y	1 294	28.7340	65.7128	48.1	Dominated ^e	Dominated ^e
Conventional cytology, 3-y	1 334	28.7344	65.7111	50.3	Dominated ^e	Dominated ^e
Combination strategy, 3/5-y	1 561	28.7380	65.7259	75.4	84 000	112 000
Combination strategy, 3-y	1 589	28.7381	65.7299	76.8	Dominated ^e	Dominated ^e
Conventional cytology, 2-y	1 743	28.7377	65.7306	65.1	Dominated ^d	Dominated ^d
Combination strategy, 2-y	1 918	28.7400	65.7374	85.1	180 000	206 000

”^aTotal discounted and undiscounted health effects is presented as life expectancy between age 15 and age 85 years, defined as LYG. ^bThe ICER for a given screening strategy was calculated relative to the next most effective strategy after eliminating dominated strategies expressed as € per LYG. ^cICER with the inclusion of cost of added life-years. Strategies that are dominated are more costly and less effective than another strategy. ^dStrongly dominated strategy (i.e., strategy that were more costly and less effective than others). ^eWeakly dominated strategy (i.e., strategy whose costs and benefits were improved by a mixed strategy of two other alternatives).”

5.2.3 Sensitivity analyses

Results were most sensitive to changes in the accuracy of the test used in the different screening strategies and their associated costs and least sensitive to variation in costs for treatment of cervical cancer. However, under most variations of model parameters and additional scenario analyses, the combination strategy at a 5-year time interval remained cost-effective.

5.2.4 Discussion

Self-sampling eliminates the need for a visit to a clinic, and enables genotyping, which makes the practice less aggressive than a gynecologic examination offered to all women with test results showing any abnormality, which is associated with high direct medical costs, direct non-medical costs and indirect costs (data shown in Paper III and Paper IV). Also, negative physical and psychological effects are associated with a more aggressive approach (233, 234). However, for self-sampling performed by the women themselves to be successful, the acceptability among the population must be high and they must comply with screening recommendations. One study found that more than half of the women in the study group (61%) preferred self-sampling at home instead of clinic based screening as long as self-sampling taken by the women themselves has the same health effect as a clinic-taken test, this due to greater ease and less inconvenience for the women in their everyday life (140).

Previous research has indicated that HR-HPV self-sampling performed in the privacy of the home is a feasible alternative for non-participants in clinic-based screening programs, the “hard-to-reach” women and women generally reluctant to undergo vaginal examination (109, 110). Overall, it could potentially increase the participation rate of organized screening (111). However, European and international guidelines do not yet recommend self-sampling in organized screening. This due to lack of evidence of higher accuracy, or as high accuracy (sensitivity and specificity) with self-samples performed by the women themselves than with samples taken by a clinician among today’s available HR-HPV self-sampling tests. According to a recent Meta-analysis of almost 40 studies with data from approximately 150 000 women found that average sensitivity for detection of CIN2 was 76% and for CIN3 84%, while specificity for CIN2+ was 86% and for CIN3+ 87% (113). Samples taken by a clinician showed overall higher accuracy than self-sampling performed by the women themselves. HPV self-sampling using signal-based assays was both less sensitive and less specific than sampling by a clinician. However, some PCR-based (polymerase chain reaction, a technology that selectively amplifies a target sequence of DNA) HPV tests showed similar sensitivity between samples collected by the women themselves and those taken by a clinician. Overall conclusions from the Meta analysis were therefore, that organized screening programs that intent to use signal-based assays (cell-based assays) should preferably be taken by a clinician. Some PCR-based HPV tests could however be considered after thorough pilot studies to assess feasibility. Present study was modeled based on accuracy data from a study examining HR-HPV among women, using PCR-based HPV tests (114-116). Regardless of sample technique, the feasibility of HPV testing for use in primary screening has been subject to discussion mainly because of its overall low specificity when used as a single HPV test, especially among young women, where HPV testing could lead to over-diagnosis of regressive CIN2 (104). Result from the clinical study found that repeat HR HPV testing at short intervals increased specificity for detection of CIN2+ lesions from about 94.2% to 97.8%. Due to lack of data from large-population based studies on accuracy of self-sampling by the women themselves vs. samples taken by a clinician and compliance with screening based on self-samples, this study made necessary assumptions of compliance rate and follow-up of HPV positive results. This has yet to be examined in real-life settings before deciding up on reframing the organized screening

program for cervical cancer. However, primary HPV testing has proven more effective than primary screening with cytology in reducing both cervical cancer incidence and mortality (88, 91, 107). The risk of CIN3 or cervical cancer is lower 5 years after a negative HPV test than 3 years after a negative cytology test, thus the HPV test has a higher NPV (92). This altogether implies the need for further clinical studies and health economic evaluations of available self-sampling tests within the framework of the organized screening program.

According to Briggs et al. (2001), every economic evaluation is subject to degrees of uncertainty or methodological controversy arising from discordant analytical results, data requirements, need to extrapolate results over time and a desire to generalize results to other settings (55, 70). Choice of modeling technique and model structure depends on availability of data for the analysis. Preferable, a systematic review of the literature should be conducted to decide up on data of importance for inclusion to the model. Due to lack of data on test accuracy, compliance with self-sampling within the framework of organized screening and the natural history of HPV, cervical dysplasia and cervical cancer, as well as survival from cervical cancer (long-term research), no specific rules were applied for inclusion or exclusion of data. Instead, best available published data appropriate for the model was initiated and decided up on within the group of clinical experts and co-authors in this study. The validity of the model was then tested by controlling for the primary and intermediate outcomes projected by the model. The “do-nothing” alternative (i.e. no screening and cervical cancer is only detected by symptoms) was applied to validate the primary and intermediate outcomes of the model. Regarding the primary outcomes, the age-specific incidence rate of HPV infection applied into the model were varied within a plausible range and computed the Markov model so that the projected outcome result resemble the average annual cervical cancer incidence rates by 5-year age groups before screening was initiated in Sweden, and thereby constructed the reference strategy “no screening”. The cytology-based screening strategy was then applied and model projected outcomes were close to empirical data after implementation of the cytology based screening program until 2009. Moreover, important intermediate projected outcomes were age-specific HPV prevalence among women with normal cytology test age-specific peak prevalence of CIN; HPV prevalence in older women all of which was similar in previous clinical trial studies and observed in a Swedish population (114, 224, 235). The referral rate for a gynecological examination with colposcopy and biopsy without presence of cervical dysplasia was 35% higher for the combination strategy at the 3/5-year interval compared with the fixed 5-year interval which is similar to the results from another model projection (232). Additionally, outcome model parameters were varied within relevant range in the sensitivity analyses and additional alternative scenarios were applied to explore the impact on cost-effectiveness. However, according to the results from the sensitivity analyses, the combination strategy at 5-year intervals remained a cost-effective alternative while other follow-up strategies remain dominated.

Overall, our model projected outcomes showed that the combination strategy with a 5-year time interval is potentially cost-effective compared with current screening practice and no screening when using a commonly used threshold value (€80 000). Even though model studies are simplifications of real-life settings, the alternative comparison with conventional cytology reflects current screening practice in real-life settings in accordance with the

aforementioned flowchart. Moreover, the follow-up and treatment of cervical dysplasia and cervical cancer associated with both alternatives also reflect the real-life setting. A transition to HR-HPV DNA testing is underway in Europe and research on the feasibility of HPV self-sampling and evaluations of their consequences on costs and value of health gains are of relevance for making informed decisions about a revised organized screening program for current and future generations in need of screening to prevent cervical cancer.

Few other studies compare self-sampling with conventional cytology and no such comparison has as yet been made within the framework of organized screening programs. One study, similar to ours, based on a US clinical trial evaluated the cost-effectiveness of self-sampling performed at home and found that in combination with follow-up of HPV positive women by use of clinical based cytology was cost-effective in comparison to clinic-based cytology screening alone (48). Our study indicated that the combination strategy at 3/5-year intervals and at 5-year intervals was cost-effective, in accordance with previous studies on clinic-based HPV testing, though not involving self-sampling at home (135, 228, 230). One study argued in favor of HPV testing in primary screening (138). Our own previous cost-effectiveness study (Paper I) found that HPV triage was superior to cytology screening for management of women aged 30 years and older with initial diagnose ASCUS. Regarding number of screening opportunities throughout a woman's lifetime, one study in a Swedish setting concluded that HPV testing combined with cytology on three occasions during a lifetime was optimal (236). In our study, lower referral rates were associated with a 5-year screening interval than with a 3/5-year interval. These findings are similar to the results of other studies, indicating that less frequent screening could reduce unnecessary follow-up and treatment and provide cost-savings with equal or more effective outcomes (232, 237, 238).

5.3 BARRIERS TO AND FACILIATORS OF COMPLIANCE WITH CERVICAL CANCER SCREENING (PAPER III)

5.3.1 Sociodemographic characteristics

According to the results on the sociodemographic characteristics of the 1510 respondent women in the study, few were associated with low SES. A comparison with the general female population in Sweden showed that a significantly higher proportion ($p < .01$) of respondents had an education level above high and higher income level.

5.3.2 Time and travel cost and other direct non-medical costs

The estimated average waiting time was 10 minutes and the procedure time was 13 minutes, for a total time at the outpatient clinic of 23 minutes. Average travel time to the outpatient clinic was 18 minutes and 26 minutes from the clinic, for a total travel time of 44 minutes. Over half the women (53%) reported officially taking time off work to attend screening, with a mean time of 2.5 hours. Among all women, approximately 12% were accompanied by a companion to attend screening, the majority by their partners. Among all companions, almost 60% had taken time off work, an estimated mean time of almost 2 hours. Among all women, almost 3% had arranged for childcare. Paid childcare was estimated with a mean time of almost 3 hours for an estimated cost of approximately €78. Overall mean total cost per attendance, including a companion, if any, was almost €56.

5.3.3 Compliance

In all, 44% of women stated that they were unlikely to attend screening within one year of the initial invitation (noncompliers), 51% of whom stated that they *could not take time off from their jobs*, while 33% stated they were *too busy* and 16% cited other reasons. Qualitative data from responders indicated that other reasons could include fear of gynecological examinations, postponing the visit due to menstrual period, pregnancy at the time of the invitation and more.

5.3.4 Knowledge of HPV

In all, almost 70% of respondents knew that screening was meant to prevent cervical cancer, while 30% believed that cytology testing was used to screen for all or other gynecological cancers. Almost half of the respondents were satisfied with the invitation letter while almost 30% were unsatisfied and others were either partly satisfied or answered “don’t know”. Compared with women aged 30-49 years, a significantly higher proportion of women aged 29 years or younger knew that HPV is sexually transmitted (51% vs 39%), that both men and women can be infected (30% vs. 24%) and that HPV is most common among young adults (37% vs. 27%). Women aged 29 years or younger also knew that HPV infections often had no symptoms (41% vs 35%); that persistent HPV infection may lead to cervical cytological

abnormalities (54% vs 48%); and were more aware that HPV can cause genital warts (24% vs 22%). Of all women in the study group, 64% knew that an HPV vaccine is available, but fewer were aware that the vaccine is most effective if administered before sexual debut (41%) and that the vaccine does not protect against all HPV types, therefore making it important to continue to attend screening (34%). However, only 7% believed they had a good knowledge of HPV and cervical cancer, and only 16% felt they had a good knowledge of HPV and cervical cancer prevention. A majority of women (63%) expressed a desire to learn more about HPV infection, risk factors and prevention from a midwife or physician, while 52% wanted additional information from brochures.

5.3.5 Factors associated with compliance and knowledge of HPV

Age, education, and income were the most important correlates of HPV knowledge and compliance; and additionally factors for compliance were time off work, companion and HPV knowledge. Women that took time off work to attend screening were less likely to be compliant with screening within one year from initial invitation. Moreover, women with knowledge of HPV were more likely to comply with screening.

5.3.6 Discussion

This descriptive study investigated barriers that may hinder participation in health-promoting behavior, since perceived benefits must outweigh perceived barriers in order for behavior to change. With continuous pressure on efficient allocation of health care resources to maximize health outcomes, decision-makers are concerned about ensuring that both the clinical effectiveness and cost-effectiveness of preventive health care are continuously evaluated (239). More often, direct-medical costs are used in health economic evaluations while direct non-medical and indirect costs less frequently are included and often overlooked (240). However, a societal perspective (i.e. a broader perspective) is recommended to assess the cost-effectiveness of treatments or preventive measures in health care (55). By using a societal perspective including direct medical costs, direct non-medical costs and indirect costs, the risk of sub-optimization decreases compared to if the analysis was carried out from a more restricted perspective. Therefore, use of societal perspective in health economic evaluations where costs incurred by different agents are included and compared is a preferred option. Important is therefore to identify all possible costs incurred by attending a clinic-based screening visit.

Moreover, indirect costs and direct non-medical costs may affect compliance with preventive health services such as screening. Since the effectiveness of a cervical cancer screening program crucially depend on women's attendance or compliance, these factors are highly important to identify. The literature suggests that high prices or time and travel costs deter purchase or use, while low prices encourage adherence to recommended preventive health services (174). Overall it should be acknowledged that even when a preventive health system offers free screening, all eligible individuals will incur costs for time and travel that are not reimbursed by public funds. Depending on their terms of employment, individuals may lose

income due to absence to attend screening and if they perceive their time and travel costs as high, they may choose not to attend screening (241-243). In Sweden today, copayment for screening services ranges from zero to about €22, depending on county council of residence. However, even when screening is offered free of charge, women will still consider the necessary time and travel costs, as well as other direct non-medical costs, which may deter them from using screening services. The importance of cost in relation to screening compliance was shown in 2003 when Stockholm introduced a screening fee of €14 per visit, resulting in a 23% decline in the attendance rate, which then recovered after the fee was discontinued (244). A disproportionate number of women in our study were high income earners compared with the eligible screening population at large, possibly indicating that women with lower incomes perceive their time and travel costs as being relatively higher, which may deter screening. Moreover, a large proportion of all responders were noncompliers, of whom many cited difficulties taking time off work. This may also imply that the disproportionate number of women with high income and high educational level in our study also perceive their time and travel costs as high, for which reason they choose to attend at a later time or when convenient in everyday life.

Other studies support our findings that indirect costs and direct non-medical costs are significant in relation to direct medical costs (242, 245). Our study concluded that mean costs per attendance were somewhat higher in this study than in another study of clinic-based cervical cancer screening in the UK (246). This difference may be explained by a longer average time for the clinical visit and the fact that more women took time off work. Moreover, leisure time was valued at about half of our estimate. If our analysis were carried out using their value for leisure time and excluding the extra cost of time off work beyond the estimated time for travel and the screening visit (approximately 1 hour), our study presented similar cost estimates. This highlights the importance of context-specific calculations when estimating indirect costs and direct non-medical costs. Women attending with a companion and women who arranged for paid child care substantially increased mean costs. The choices to be accompanied by a companion and child care are not addressed by our data, but these factors have an important impact on cost.

Use of self-sampling could reduce overall sampling costs but also affect coverage (158, 173, 247). HPV self-sampling as alternative screening, with no costs for time and travel, may increase compliance among those women who perceive time and travel costs to be high. Use of HPV test enables longer time intervals between screening since the risk of developing a CIN3 or cancer after five years is lower after a HPV negative test result than a negative Pap test. The longer time intervals between screening opportunities enabled by HPV testing will affect the population coverage by changes in the definition of test coverage. Also, longer screening intervals can increase the coverage for the hard-to-reach women and an under screened population and also acceptable to a disadvantaged group of women (170, 173, 248-254). In Sweden, Uppsala County Council has successfully increased overall participation in the screening program by introducing a self-sampling device as an alternative screening method (110, 114). One study in the Finnish cervical cancer screening programme involving non-participants showed that HPV self-sampling could lead to higher participation rate and protective effect among those women (255). However, there is also a concern (mostly speculative) that use of HPV tests will affect the women's behavior and attitudes towards

screening. Suggested is that the longer interval may impact on women's behavior and therefore have a negative effect on coverage and especially among women with low SES (248). However, information on cues to action, necessary for prompting engagement in health-promoting behavior, particularly in regard to the uptake of screening with self-sampling is lacking and further research on this is needed.

HPV-self sampling may be a preferred option specifically in low-resource settings where there is restricted infrastructure which lowers the effectiveness of clinical based-cytology screening programmes. This due to the fact that women in these settings will be screened only a few times in their lives and the high sensitivity of a HPV test is important. Although, there are concerns about women not receiving the home-mailed self-sampling devices due to different reasons either in mailing lists or logistic reasons (173, 250). The effectiveness of self-sampling depends heavily on updated and correct register data. However, use of this method in countries with well-organized screening programs, such as Sweden, could possibly increase access to screening both for those reluctant to undergo a gynecological examination and women "hard to reach" and thereby improve the overall participation and the inequitably among women with low SES.

According to previous research, women with low education level or SES and certain disadvantaged ethnic groups are less knowledgeable about HPV infection and associated risks of developing cervical dysplasia and cervical cancer (256-259). In European countries, studies have shown that women with higher educational level were more knowledgeable of HPV than those with lower educational level and an association with SES (150, 151). Many of the studies that have been conducted were performed before the introduction of the HPV vaccine (before 2007-2009). Knowledge of HPV has most likely increased since then. Also possible is that women with lower educational level could have increased their knowledge far more than women with higher education. Previous studies on awareness and knowledge of HPV in Europe since the introduction of the mass vaccine have shown various results on knowledge and attitudes towards vaccination. One study found that knowledge about cytology with Pap smear were higher than knowledge about HPV test but still a large proportion knew about the transmission of viruses, HPV and its relation to cancer (260). This study also found that women with higher educational level were more knowledgeable of cervical cancer, prevention methods and HPV. However, attitudes towards HPV vaccination were alike among all women regardless of educational level. In our study, women with low SES was less represented however there was a clear association between HPV knowledge and education level. Women with higher education were more knowledgeable about HPV than those with lower education level.

Additionally; age was also one of the most important correlates of HPV knowledge. Most importantly, we found that young adults were more familiar with HPV than older women; they knew more about HPV prevention methods, including HPV vaccination, even though no statistical difference was found between the age groups. This implies that inclusion of HPV vaccination in the school vaccination program may have an impact on the level of knowledge about prevention in both younger and older age groups. Earlier targeted information and commercial campaigns prior to this study may have increased knowledge of HPV, but to what extent is unclear.

In our study, a majority of women wanted information about HPV and preventive methods to be provided by through personal counseling by a midwife or physician. Previous research aiming to provide insight into effective communication tolls has shown that differences in knowledge about HPV decrease following any type of intervention or informative public campaign (261-265). However, further knowledge about effective communication tools and how to increase knowledge with populations about HPV is needed. Further, there is often an absence of information regarding SES in studies of effective communication tools. Further knowledge about SES and how to reduce the SES inequalities is therefore needed.

In summary, the most important correlates for compliance were age, education, income, time off work and knowledge of HPV, while the most important correlates for knowledge of HPV were age, education and income. This suggests that knowledge of HPV and its relationship to cervical cancer promotes/facilitates compliance. Knowledge of HPV is a factor that can be directly assessed through public education using campaigns and personal counseling with the midwife or gynecologist.

5.4 COST OF PREVENTING, MANAGING AND TREATING HUMAN PAPILLOMAVIRUS (HPV)-RELATED DISEASES BEFORE THE INTRODUCTION OF QUADRIVALENT HPV VACCINATION (PAPER IV)

5.4.1 Cost for screening, management and treatment of CIN and cervical cancer

From a societal perspective, the estimated economic burden of cervical dysplasia was €75 million, €8.5 million of which consisted of costs for colposcopy and biopsy referrals and € 6 million of treatment costs. Based on data showing that 441 women in Sweden were diagnosed in 2009 with incident cervical cancer, and 9 651 prevalent cases and 158 women died from the disease costs for staging and treatment and follow-up of these cases resulted in an annual cost of €23 million, 20% accounted for palliative care. The economic burden attributable to HPV related diseases cervical dysplasia and cervical cancer was €98 million.

5.4.2 Treatment patterns for genital warts

The treatment patterns and percentage of patients with external, external and internal, or internal genital warts did not differ by gender. The majority of patients with incident external and external and internal genital warts received pharmacological treatment (topical creams), while the wait and see approach was assessed for the majority of patients with only internal genital warts. Overall, destructive treatment was more common among recurrent and persistent cases of genital warts in our study. Estimated mean time for office visits in the absence of destructive or surgical treatment was 22 minutes, and an estimated 31 minutes when destructive or surgical treatment was provided. The average number of visits needed for incident and recurrent patients with pharmacological treatment, destructive treatment, combination treatment, or surgical treatment was estimated at: 2, 2.5, 2.3 and 1.6, respectively. Based on data from a published study, the total number of incident cases of genital warts (seeking or receiving treatment) in Sweden was estimated to be 18 196 in 2009 (220). Based on data from the United Kingdom, there were an estimated 10 548 recurrent and persistent cases of genital warts in Sweden according to our extrapolation (221). The average estimated percentage of patients with external genital warts only was 87%, while 10% had both external and internal genital warts and 3% internal genital warts only.

5.4.3 Cost for management and treatment of genital warts

The total cost of 28 744 cases of genital warts in 2009 was €9.8 million. The total annual cost of treating external genital warts was estimated at €8.1 million, while costs for external and internal genital warts were estimated at €1.2 million, and internal genital warts alone at €0.5 million. Of the total cost, that of pharmacological treatments was estimated at €2.9 million, while destructive treatment was €3.4 million. Costs for surgical excision were €1.9 million

and combination treatment €0.9 million. The total cost of management and treatment of recurrent and persistent cases alone was €4.5 million. In the sensitivity analyses we lowered the direct costs for a visit to a physician and treatment by 50% to reflect possible outpatient costs. This decreased the total cost of treatment of genital warts by €3.8 million (39%).

5.4.4 Total annual cost for cervical dysplasia, cervical cancer and genital warts

The total estimated costs for the prevention, management and treatment of HPV related diseases namely cervical dysplasia, cervical cancer and genital warts for 2009 was €108 million, and ranged from €66 to €121 million depending on sensitivity analyses.

5.4.5 Discussion

The number of cases of cervical cancer was obtained from the IARC. However no data are available on FIGO staging, whether patients had concluded treatment, relapses or survival rates related to various FIGO stages. To avoid duplication between cases, we considered only follow-up costs for prevalent cases and estimated treatment costs for new cases. Similar problems arise regarding the number of patients with cervical dysplasia and genital warts, for which register data are lacking or unavailable. Data inaccuracies or the need to make assumptions may have led to certain underestimation or overestimation of costs.

When estimating treatment patterns for management and treatment of genital warts, the clinical expert panel was asked to answer based on experience, rather than by referring to patient charts, which may have led to biased estimate of costs. Moreover, the estimated number of recurrent and persistent cases of genital warts was based on a UK publication (221). Swedish data would of course more accurately reflect the situation in Sweden, but no such data has yet been published. Furthermore, register data do not reflect nuances in treatment of genital warts. However, incidence rates are possibly underestimated since primary cases that do not receive pharmacological treatment would not be included (220).

Travel time to and from healthcare facilities was based on estimates from Stockholm (Paper III), which may not be representative of the entire country; costs may be underestimated for geographical areas involving greater distances and consequently more costs.

However, our findings give important insight to HPV-related diseases in Sweden which has previously been unknown. Despite limitations of this study, these results are of interest due to the recent introduction of the quadrivalent HPV vaccination (against HPV6, 11, 16 and 18) program among school girls. In clinical trials, the quadrivalent vaccine has shown to reduce lifetime risk of cervical cancer caused by the corresponding HPV types by 47%-100%, depending on age (i.e. girls being HPV naïve when vaccinated) and coverage (266, 267), and to reduce the risk of genital warts by 83% (268). A significant reduction in the future economic burden of management and treatment costs for CIN, cervical cancer and genital warts is expected due to factors such as an unchanged organized cervical cancer screening

program and added quadrivalent HPV vaccination for young girls. Previous cost-effectiveness analyses have shown that adding a quadrivalent HPV vaccine to an existing cervical cancer screening program is cost-effective (269-271). The WHO funded PRIME modeling study, found that in 156 of 179 countries, prophylactic HPV vaccination in girls, HPV naïve at onset of vaccination is very cost-effective (271). Sweden was, in spite of a relatively low incidence and mortality of cervical cancer, one of these countries. Important to consider were that the effects of genital warts were not taken into account in this analysis. However, further studies on the effect of HPV vaccine on other HPV-related diseases needs to be evaluated. Moreover, further modeling studies are needed to fully evaluate the cost-effectiveness of the quadrivalent HPV vaccine and the upcoming nine valent HPV vaccine. The implementation of organized prophylactic HPV vaccination in Sweden may lead to an evolution where a greater portion of resources are allocated to prevention and a decreasing portion allocated to manifest disease management.

Questions that remain to be answered is whether boys be included in the organized HPV-vaccination program, and how to wisely design the Swedish cervical cancer screening program to adapt to a future generation women with a lower incidence and prevalence of precancerous lesions and genital warts. With the future implementation of a nine valent vaccine, expected reduced incidence of cervical cancer will lead to a situation of cervical cancer being a rare disease while other HPV related diseases such as tonsillar carcinoma is expected to increase, and especially among men (272). Hammarstedt et al demonstrated the increasing incidence and the proportion of HPV-positive tonsillar cancer and authors hypothesized an “epidemic” of HPV-infection in the oropharynx (273). Although this study only assessed few of the HPV-related diseases, these diseases account for a majority of the total economic burden attributable to HPV type 6, 11, 16 and 18 infections this study gives important information on the potential savings if these major diseases were eradicated in the future. Moreover, costs from this study may be incorporated into future cost-effectiveness analyses comparing strategies with different available HPV vaccines, and alongside the existing and a potential revised cervical cancer screening program including HPV tests.

A recent study from Italy concluded that the estimated economic burden for 9 HPV related diseases namely cervical cancer, cervical dysplasia; cancer of the vulva; vagina; anus, penis, head and neck; genital warts and recurrent respiratory papillomatosis were a total of €529 million (with a plausible range of €480-€686 million) (expressed in 2011 Euro) of which HPV types 6, 11, 16 and 18 accounted for 55% of the total cost (274). In the Italian study, only direct medical costs were included from the perspective of the National Health Service. Of the total sum, €147 million represented direct medical costs for cervical conditions alone. Also, the economic burden of non-cervical, HPV-related diseases born by men were identified as cost drivers highly important to consider when deciding up on future preventive programmes to further reduce HPV prevalence among the population. This study highlights a significant economic burden associated with the most prevalent HPV-related diseases in Italy. However, similar estimates are expected in every country with similar health care system and preventive health care programs for cervical cancer. Our study only provides a partial estimate of the cost of HPV-related diseases. Other HPV-related diseases were not included and have yet to be further evaluated.

The economic burden of cervical cancer and genital warts is somewhat higher than found by other studies carried out in Europe (275) (276, 277). However, similar estimates were made in Belgium, where estimated annual screening costs from a societal perspective were almost €65 million with an additional 16 million for management of cervical cancer, cervical dysplasia and genital warts (10.5 million inhabitants) (278, 279). The differences of unit costs across countries may be related to possible overestimates in the present study. First, direct medical costs for an initial visit for cytological testing reflected the costs for a hospital of which the aforementioned studies reported half of the direct medical cost for a Pap smear visit. Although when we decreased in the cost of an initial visit with 50% and number of colposcopy referrals reduced the total annual cost to similar estimations previously presented in the aforementioned studies. However, actual costs for a visit for medical procedure in an outpatient clinics has yet to be examined to accurately determine a possible lower cost. However, compared with other studies, the overall treatment costs for genital warts in our study were similar to those from other studies (280, 281).

6 CONCLUSIONS

6.1 PAPER I

In Sweden, approximately 650 000 cytology test are performed every year, of which around 5% show any cytological abnormalities (80% are diagnosed ASCUS/-LSIL and 20% HSIL) and are in need for further follow-up and management. Our study result concluded that an additional 85 cases of CIN2+ could be detected per one thousand women with index smear diagnosis of ASCUS or LSIL per year if immediate colposcopy with biopsy was used for all of these women instead of repeat cytology. This translated into approximately 2 000 additional CIN2+ cases detected compared with the use of repeat cytology. Compared to HPV triage, immediate colposcopy with biopsy would detect approximately 1 000 additional CIN2+ cases. Alternative follow up strategy is especially important since an estimated 5 to 30% of missed CIN2+ cases could progress to invasive cancer. However, use of colposcopy and biopsy is a more aggressive approach which is associated with risk of over diagnoses and overtreatment of women not truly at risk of developing cervical cancer. Moreover there are concerns about adverse events which may apart from the physical and psychological distress have important economic impact that needs to be addressed. Therefore HPV triage could be considered a less aggressive approach. In this study, our results show that HPV triage is a preferred alternative follow-up strategy compared to repeat cytology for follow-up of index smear diagnosis of ASCUS/-LSIL among women over 30 years of age. For women 30 years and older with index smear diagnose of ASCUS alone, HPV triage was the least costly alternative with equal health benefits as repeat cytology. Current Swedish guidelines and practice for women with ASCUS/-LSIL/CIN1 are HPV triage on women 35 years and older. Results from this study concluded that HPV triage is the least costly follow-up strategy among women 30 years and older with index smear diagnose of ASCUS, however the specificity of HC2 needs improvement.

6.2 PAPER II

The combination strategy involving use of cytology testing between the age 23 year and 34 and thereafter HPV self-sampling performed by the women themselves at home with a 5-year screening interval is potentially cost-effective compared with no screening, and with current screening practices when using a threshold value of €80 000 per life-year gained. With recent research showing that the risk of cervical pre-cancer is low up to 5 years after a HPV negative test, implies together with this study result that HPV testing in primary screening from 35 years and older could potentially be a both clinical effective and a cost-effective approach. Health care resources should preferably be allocated to women with HPV 16 and HPV 18 positive results which have the highest risk of developing cervical pre-cancer. Further pilot testing of HPV self-sampling tests and research on acceptance and compliance with self-samples in larger population based studies has yet to be performed to

make better-informed decisions on reframing the organized screening program.

6.3 PAPER III

We found that time and travel costs and other direct non-medical costs are substantial and may deter women from attending and may also influence the overall cost-effectiveness of a screening program. A large share of the responders was noncompliers with screening within one year of the initial invitation. Knowledge was higher among women in the younger age groups. Age, education, and income level were the most important correlates of HPV knowledge, while additional, hours off work, accompanying companion and knowledge of HPV were important correlates of compliance. Through public education programs, knowledge of HPV could be increased on population level and thereby promote/facilitate compliance with screening. Given that the effectiveness of a population based screening program depends on participation and compliance, both knowledge and low or no cost for the women to attend screening are both important factors that needs to be considered. All barriers for compliance with screening should be addressed and taken into account within the organized screening program.

6.4 PAPER IV

A cost-of-illness study estimates disease-specific costs, and provides information on the maximum potential savings that could be done if a disease were to be eradicated. From a societal perspective including both direct medical costs and indirect costs, we found that the estimated economic burden of HPV related diseases namely cervical dysplasia, cervical cancer and genital warts were a total of €108 million. Costs for screening, management and treatment of cervical dysplasia were €75 million of which costs for primary screening and inadequate tests alone accounted for the majority of this sum and management and follow-up of abnormal cytology results were estimated to account for around €11 million of the total costs while costs for treatment of CIN accounted for a minor cost. Estimated costs for recurrent and persistent cases of genital warts were around €10 million. In the sensitivity analysis, costs were most sensitive to variations in screening costs. This implies that any changes in the existing organized screening program may have large impact on the overall costs. The results provide an estimate of the significant economic burden imposed by three major HPV-related diseases; cervical dysplasia; cervical cancer and genital warts in Sweden. There should be further evaluations of the economic burden of the other HPV-related diseases; cancer of the vulva, vagina, anus, head and neck, penis and recurrent respiratory papillomatosis. Future evaluations should also consider both men and women to fully understand the cost drivers.

7 FUTURE RESEARCH

Payers for health care are continuously searching for value for money from health care interventions, in an effort to achieve the best possible health and health care within available resources. Since there always will be more alternatives than resources will allow, choices and trade-offs needs to be made. Health economic evaluations are therefore important information to aid decision making about the allocation of resources to technologies. However, an important question for conducting economic evaluations is if there is documented clinical evidence existing for the disease and alternative preventive methods and treatments. These data will assess the quality of the economic evaluation. Still there is knowledge gaps that need to be addressed in future research.

Firstly, there is currently a lack of data on prevalence of HPV infection among the Swedish population which needs to be addressed. There are only limited data from the previous Swedescree- study (1997-2000) targeting women between age 32 and 38.

Further, primary HPV-based screening is gradually being introduced throughout Europe as in Sweden. Future research should within the preventive program confirm that HPV testing with triage cytology will increase detection of CIN2+ compared with conventional cytology alone, result in fewer follow-up procedures and less unnecessary treatment.

There are concerns regarding recurrent disease in women diagnosed and treated for CIN2+. Among these women, Meta-analyses of previous studies indicate an increased risk of adverse birth-outcomes for women of fertile age. Cold-knife conization in particular was associated with increased risk of perinatal mortality, extreme preterm delivery and low birth weight. Future research should therefore focus on gathering data on the long-term effects of current treatment options for CIN. Women diagnosed with CIN are at higher risk of subsequent cervical cancer. Follow-up strategies appropriate for decreasing the risk of or development of cancer in these women should therefore be evaluated. These data should all be incorporated into cost-effectiveness studies to confirm the cost-effective combinations of screening including management and treatment of CIN, follow-up strategies and birth outcomes in order to minimize risks and maximize the health benefits of cervical cancer screening programs.

Switching from current conventional cytology screening to HPV testing for primary screening has raised concern about possible low compliance with a 5-year screening interval after a HPV-negative test compared with the current 3-year interval following a negative cytology test. Currently, no studies have been published on compliance with the specified 5-year interval after an HPV-negative test. Therefore, future research should be conducted on compliance with screening protocols, both in clinical trials and through register-based data. Another important subgroup in the new screening protocol using primary HPV-DNA testing relates to women who are HPV-positive and cytology negative. Previous studies have shown that such women prefer to be examined immediately with colposcopy. Future research should be performed on this subgroup to investigate barriers (induced anxiety, low awareness and knowledge of HPV, risk factors and their relationship to diseases) and facilitators (increased

awareness and knowledge of HPV) of compliance with screening protocols adjusted for this subgroup.

In addition, the potential of infecting others with HPV may pose new problems with anxiety related to sexually transmitted diseases that are linked to development of any HPV related cancer. Research should also be conducted on effective communication tools for HPV-positive women to reduce unnecessary colposcopies and biopsies, as well as overtreatment of regressive CIN, which is a risk if reassurance is not effectively communicated.

Facilitators and barriers are related to knowledge and the ability to comprehend the message communicated by health professionals, which ultimately relates to educational level. Further research should therefore be carried out on correlates of compliance with screening protocols. Research should therefore focus on providing insights into effective communication tools about HPV, and how to reduce SES inequalities.

Future research should consider the feasibility of HPV self-sampling devices for screening of the two most relevant subgroups: non-participants, hard-to-reach women. Furthermore, HPV self-sampling may reduce screening costs however further research on this is also needed. Equity of access to health care is a major concern. HPV self-sampling could potentially reduce inequity of access provided that the healthcare system can access all women through postal services. Concerns are about those women that cannot be reached at their home. Therefore, other ways to reach women such as pick up self-sampling devices at pharmacy or other local services should also be considered within the framework of the organized screening program and further Evaluated.

This thesis explored annual costs in Sweden of the HPV-related diseases cervical cancer and genital warts. Our estimates were partly based on assumptions since there is little data concerning on epidemiology and costs linked to HPV related diseases in Sweden. To understand the societal costs of HPV-related diseases, proper cost-of-illness studies must be conducted in which detailed information on resource use and productivity is gathered concerning all major HPV-related diseases, including cervical dysplasia, invasive cervical cancer, genital warts, cancer of the vulva, vagina, anus, penis and head and neck and recurrent respiratory papillomatosis and any other diseases that may be linked to HPV in the future. How various HPV types relate to different diseases in terms of etiology and epidemiology also needs further investigation.

In future generations, the upcoming nine valent vaccine is expected to prevent 90% of cases of invasive cervical cancer among HPV naïve women. Recent results from vaccine studies showed high vaccine efficacy against CIN2+ in women with serological evidence of past HPV infection but no active HPV infection at the time of vaccination. This suggests that these women who solely relies on screening as preventive method could potentially benefit from HPV vaccination in the future. However, until then, cervical cancer screening must continue since vaccination offers no protection against those HPV types not included in the first-generation vaccines. Since there will be a lower incidence of precancerous lesions and cervical cancer diseases as an effect of the HPV vaccination program, the current approach using frequent cytology-based screening will not be considered cost-effective. Therefore,

further research should focus on new alternative screening technologies and protocols for these subgroups. Also, future research should focus on the question whether to include boys into the vaccination programme. As new data become available, cost-effectiveness analyses should be updated with vaccine-related parameters in order to confirm the preferable screening approach for both vaccinated and unvaccinated women. When replacing older interventions with new ones, decisions about allocations will have to be based on formal evaluations of the additional health benefit is worth the additional cost.

In summary, all of the above mentioned suggestions for future research are crucial to maximize health benefits of screening, while minimizing the risks of women being over-screened, over-diagnosed and consequently over-treated. All of the above suggestions can be followed up within existing national register-based data to prevent cervical cancer.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Livmoderhalscancer är en angelägen fråga, både humanitärt och ekonomiskt för hela världen. Utifrån forskningen är det nu väl känt att livmoderhalscancer orsakas av Humant Papillomvirus (HPV), som är en sexuellt överförd infektion. HPV är den vanligaste sexuellt överförbara sjukdomen bland unga kvinnor och män runt om i världen. Detta gör livmoderhalscancer till den näst vanligast cancerformen bland kvinnor i världen, med knappt en halv miljon fall som upptäcks och omkring en kvarts miljon kvinnor som dör varje år i sjukdomen. Majoriteten av kvinnorna som drabbas bor i utvecklingsländer. I Sverige är det omkring 450 kvinnor som drabbas och 150 kvinnor dör varje år av livmoderhalscancer. Det finns olika typer av livmoderhalscancer, som utvecklas från olika celler. Den vanligaste är skivepitelcancer som står för omkring 80% av alla fallen. Fall av skivepitelcancer i livmoderhalsen har minskat dramatiskt under de senaste årtiondena i länder som infört organiserad screening med cellprov. Den andra typen är adenocarcinoma som utgör omkring ca 20 % av alla tumörer i livmoderhalsen och utgår från körtelepitelceller. Denna form är tyvärr inte lika lätt att upptäcka med cellprov som skivepitelcancer. Dessutom vet man inte lika mycket om dess orsaker, som man vet om skivepitelcancer. Följaktligen har livmoderhalscancer av körtelepiteltyp snarare ökat under det senaste årtiondet. Infektion med Humant papillomvirus (HPV) är nödvändig för att livmoderhalscancer ska utvecklas och i nästan 100% av alla fallen återfinns HPV-16 och HPV-18, de vanligaste förekommande hög risk typerna. HPV är mycket vanligt förekommande bland både män och kvinnor och smittar vid sexuell kontakt. Den diagnostik som bedrivs med cellprovet är otillräckligt och därför blir kvinnorna idag inte sällan föremål för onödig gynekologisk utredning och överbehandling vilket i förlängningen kan påverka kvinnans psykiska och fysiska hälsa. HPV test är bevisligen mer effektiva än cellprovet att upptäcka förstadiet till livmoderhalscancer. En förbättrad diagnostik med HPV test skulle kunna öka möjligheten att upptäcka kvinnor som riskerar att utveckla livmoderhalscancer i tidigare skede.

I Sverige, med ett omfattande organiserad screeningprogram med cellprov har man sedan 2012 kompletterat preventionsarbetet med det allmänna vaccinationsprogrammet med HPV-vaccinering av 11-åriga flickor för att ytterligare minska antalet fall av livmoderhalscancer i framtida generationer. Vaccinet som används idag skyddar mot två högrisktyper-HPV 16 och HPV 18 som är klart dominerande när det gäller risk att utveckla cervixcancer men skyddar endast upp till 70% av fallen. Fortfarande finns det behov av screening för att kunna ge ett effektivt skydd mot livmoderhalscancer hos hela den kvinnliga befolkningen.

Vidare skyddar vaccinet mot HPV 6 och HPV 11 som orsakar kondylom. Kondylom utgör en av de vanligaste könssjukdomarna bland främst unga män och kvinnor. Sjukdomen utvecklar ofarliga vårtor i underlivet eller kring ändtarmsöppningen. Trots att vårtorna är ofarliga kan de orsaka klåda, sveda, små blödningar och besvär vid samlag. I en tidigare studie uppskattades att omkring 20 000 nya fall av kondylom behandlas medicinskt varje år. Detta sammantaget gör även kondylom till en angelägen fråga, både humanitärt och ekonomiskt. Utifrån tidigare forskningsresultat förväntas antalet fall minska bland unga upp till omkring 80 % med införandet av HPV vaccinet.

Hälsoekonomi är ett område, inom vilket man analyserar hälsa och sjukvård utifrån ekonomisk teori och empiri, och med metoder som specifikt utvecklats för området. Syftet med hälsoekonomiska utvärderingar är att estimerar de hälsoeffekter och kostnader som uppkommer vid införande av nya interventioner, behandlingar, teknologier eller läkemedel. Det är oundvikligt att val mellan tillgängliga alternativ måste göras då det alltid finnas mer alternativ än samhällets resurser tillåter. Besluten om allokering av resurser och byta ut gamla interventioner mot nya ska baseras på formella utvärderingar om den extra hälsoeffekten är värd den extra kostnaden för samhället.

Europeiska kommissionen ger rekommendationer om screening för livmoderhals-, bröst- samt kolorektalcancer som inte är bindande, men policypåverkande för samtliga europeiska länder. Inom EU utformas även HTA-analyser ("Health Technology Assessment") för screening (EUnetHTA) och implementeringsprogram (European Partnership for Action Against Cancer – EPAAC).

Enligt Socialstyrelsen i Sverige ska screening program för cancer uppfylla kraven på att vara både kliniskt effektiva och kostnadseffektiva innan beslut kan tas om introduktion av nyascreening program eller förändringar av befintliga. För att ett screening program ska kunna uppfylla dessa krav krävs det också att kvinnorna accepterar screening programmets utformning och går på kontrollerna enligt kallelse. Det är därför viktigt att identifiera potentiella barriärer till hörsamhet och deltagande i screening program. Utifrån den teknologiska utvecklingen av nya och idag tillgängliga HPV tester som bevisligen är mer effektiva än cellprov för att upptäcka förstadiet av livmoderhalscancer pågår en översyn av det nationella screening programmet för livmoderhalscancer. Arbetet ska vidare leda till beslut om användande av HPV tester istället för dagens cellprov i screening programmet.

Målet med denna avhandling var att undersöka kostnaden för livmoderhalscancer och undersöka vilken screening metod som potentiellt kan vara kostnadseffektiv (i.e. screening med cellprov i jämförelse med HPV test) och identifiera potentiella barriärer till kvinnors deltagande i screening programmet.

I det första delarbetet undersökte vi utifrån ett hälso- och sjukvårds perspektiv om HPV test var ett kostnadseffektivt alternativ i jämförelse med cellprovet eller en omedelbar undersökning av livmoderstappen i mikroskop med riktade vävnadsprov som uppföljning av kvinnor som hade lindriga cellförändringar vid första screening tillfället. Resultatet visade att omedelbar mikroskopi (kolposkopi) och riktade vävnadsprov var en kostnadseffektiv uppföljningsmetod i jämförelse med både cellprovet och HPV testet för att upptäcka måttliga tillstarka cellförändringar. Detta beroende till stor del på att uppföljning med endast cellprov eller HPV test är mindre effektiva metoder som leder till ytterligare gynekologisk uppföljning vid upptäckt av cellförändringar eller hög-risk HPV och därmed även högre kostnader. Direkt kolposkopi och vävnads prov har högre effektivitet och utgör endast en kostnad för *ett* besök hos läkare för diagnos innan beslut om behandling. Studien gjordes när cytologiska prover med Pap smear utgjorde större andelen av cellproverna i Sverige. Idag används mestadels vätskebaserad cytologi som möjliggör efterföljande HPV test ur samma prov. HPV testning i kombination med vätskebaserad cytologi (s.k. HPV-reflex) skulle istället kunna utgöra ett kostnadseffektivt alternativ.

I den andra studien undersökte vi utifrån ett samhällsperspektiv och inom ramen av det organiserade screening programmet om en kombinationsstrategi med cellprov hos kvinnor mellan 23 och upp till 35 år och därefter HPV-självtest till 60 års ålder var ett kostnadseffektivt alternativ till cellprovet. Resultatet visade att kombinationsstrategin var ett kostnadseffektivt alternativ i jämförelse med cellprovet och ingen screening.

I tredje studien undersöktes kostnader i samband med ett besök för cellprov, kännedom om HPV och deltagande i screeningen. Resultatet visade på en hög kostnad för produktionsbortfall och andra kostnader för resa, transport, barnvakt etc. som uppstår när kvinnan deltar i screeningen. Vidare svarade 53 % av kvinnorna att de tagit ledigt från arbetet för att delta i screeningen varav 44% angav att de inte deltar i screeningen inom 1 år från den första kallelsen pga. sin arbetets situation. Generellt hade kvinnorna låg kännedom om HPV och endast 34% kände till att det var viktigt att fortsätta gå på kontroller efter HPV vaccination. Kvinnor som uppgav att de tog ledigt från arbetet för att delta var mindre benägna att delta i screeningen inom 1 år från kallelsen. De kvinnor som hade låg kännedom om HPV deltog inte heller i lika stor utsträckning som de med högre kännedom om HPV. Viktigt var också att kvinnor med låg SES var mindre representerade bland deltagarna.

I fjärde delstudien undersökte vi utifrån ett samhällsperspektiv kostnaderna för prevention, diagnostik och behandling av förstadier och utvecklad livmoderhalscancer tillsammans med kostnaderna för behandling av kondylom i Sverige. Samhällets kostnad innan initiering av organiserad HPV vaccinering av flickor uppskattades till omkring 108 miljoner Euro. Kostnaden för screening uppgick till omkring 77% av den totala kostnaden för livmoderhalscancer.

Fortfarande finns bristande kunskap om HPV relaterade sjukdomar och om framtida förebyggande strategier (exempelvis vaccination) som prevention vid dessa cancerformer. Vidare är prevalensen av HPV infektioner inom den svenska befolkningen är fortfarande okänd. Det finns endast data från Swedescreen-studien (1997-2000) för en begränsad åldersgrupp. Det saknas även svensk data om riskerna för att barn föd förtidigt efter behandling av dysplasier med konisering. Det saknas också information om kvinnors inställning till HPV-test jämfört med det traditionella cellprovet, detta oavsett om det tas på den lokala mödravårdscentralen eller om det tas av kvinnan själv i hemmet (s.k. HPV-självtest). Vidare saknas information om hur kvinnor uppfattar ett besked från sjukvården om att de är HPV-positiva. Frågor som också bör besvaras är hur kvinnor som är HPV-positiva med normal cytologi och HPV-vaccinerade ska följas upp i screening programmet. När HPV test införs i det screening programmet istället för cellprovet bör även effekten av införandet på kvinnors deltagande följas upp. Även användandet av HPV självtest bör följas upp inom screening programmet. Mycket av ovanstående kunskapsluckor kan följas upp i det nationella kvalitetsregistret för förebyggande av livmoderhalscancer.

En annan väldigt viktig fråga som bör utredas är om även pojkar ska erbjudas HPV vaccination. Det är för tidigt att säga om och i vilken grad en allmän HPV-vaccination av både flickor och pojkar skulle påverka flockimmuniteten mot HPV relaterade cancersjukdomar. Skyddseffekten av HPV-vaccin hos pojkar utvärderas i takt med att nya forskningsresultat blir tillgängliga. Men redan idag visar forskningsresultaten alltmer på att

HPV förekommer även i andra tumörformer som t ex huvud–halscancer och anogenitala tumörer. Man vet att HPV 16 spelar en viktig roll för ökningen av tonsillcancer som tros öka det närmsta årtiondet och speciellt bland unga män som idag står utanför barnvaccinationsprogrammet. En omprövning av om även pojkar ska vaccineras bör ske inom kort för att stävja en vidare ökning.

Sammantaget utgör denna avhandling information inför vidare beslut om förändring av befintligt nationellt screening program för livmoderhalscancer.

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